

opioid antagonists, such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, and naltrexone and those disclosed in WO00/21509; orexin antagonists, such as SB-334867-A and those disclosed in PCT publication Nos. WO01/96302, WO01/68609, WO02/44172, WO02/51232, WO02/51838, WO02/089800, WO02/090355, WO03/023561, WO03/032991, and WO03/037847; PDE (phosphodiesterase) inhibitors, such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast; peptide YY and fragments and variants thereof (e.g. YY₃₋₃₆ (PYY₃₋₃₆)(N. Engl. J. Med. 349:941, 2003; ikpeapge daspeeInry yaslrlhylnl vtrqry) and PYY agonists such as those disclosed in WO03/026591; phendimetrazine; phentermine, phosphate transporter inhibitors; phosphodiesterase-3B (PDE3B) inhibitors; phytopharm compound 57 (CP 644,673); pyruvate; SCD-1 (stearoyl-CoA desaturase-1) inhibitors; serotonin reuptake inhibitors, such as dexfenfluramine, fluoxetine, and those in U.S. Patent No. 6,365,633, and WO01/27060, and WO01/162341; T71 (Tularik; Inc.; Boulder CO); thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in WO02/15845 and Japanese Patent Application No. JP 2000256190; Topiramate (Topimax®); transcription factor modulators such as those disclosed in WO03/026576; UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]-benzoic acid (TTNPB), retinoic acid, and those disclosed in PCT Patent Application No. WO 99/00123; β 3 (beta adrenergic receptor 3) agonists, such as AD9677/TAK677 (Dainippon/Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW 427353, Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), and SR 59119A, and those disclosed in US Patent Nos. 5,705,515, US 5,451,677 and PCT publication Nos. WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO01/74782, WO02/32897, WO03/014113, WO03/016276, WO03/016307, WO03/024948, WO03/024953 and WO03/037881; β -hydroxy steroid dehydrogenase-1 inhibitors (β -HSD-1); β -hydroxy- β -methylbutyrate.

30 Anxiety related disorders

The compounds disclosed herein (for example, FAAH inhibitor compounds) can be used to treat anxiety disorder (including generalized anxiety disorder, panic disorder, and social anxiety disorder) and depression. Anxiety disorders are a group of psychological problems whose key features include excessive anxiety, fear, worry, avoidance, and compulsive rituals, and produce or result in inordinate morbidity, over utilization of healthcare services, and functional impairment. They are among the most prevalent psychiatric conditions in the United States and in most other countries. Anxiety disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Revised 1994, published by the American Psychiatric Association, Washington, D.C., pages 393-444) include panic disorder with and without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), acute stress disorder, generalized anxiety disorder (GAD), anxiety disorder due to a general medical condition, substance-induced anxiety disorder, specific phobia, and anxiety disorder not otherwise specified.

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable. The obsessions or compulsions cause marked distress, are time-consuming, and/or significantly interfere with social or occupational functioning.

Panic disorder is characterized by recurrent unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks. A panic attack is defined as a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias

(numbness or tingling sensations); and (13) chills or hot flushes. Panic disorder may or may not be associated with agoraphobia, or an irrational and often disabling fear of being out in public.

5 Social anxiety disorder, also known as social phobia, is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The
10 avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

15 Generalized anxiety disorder is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty
20 concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. The diagnostic criteria for this disorder are described in further detail in DSM-IV, which is incorporated herein by reference (American Psychiatric Association, 1994).

25 Post-traumatic stress disorder (PTSD), as defined by DSMIII-R/IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include re-experiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to
30 cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as

diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are
5 present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

It is contemplated that the compounds will be effective in treating obsessions and compulsions in patients who have been diagnosed as having obsessive compulsive
10 disorder based upon administration of appropriate tests, which may include, but are not limited to any of the following: Yale Brown Obsessive Compulsive Scale (YBOCS) (for adults), National Institute of Mental Health Global OCD Scale (NIMH GOCS), and CGI-Severity of Illness scale. It is further contemplated that the compounds will be effective in inducing improvements in certain of the factors measured in these tests, such as a
15 reduction of several points in the YBOCS total score. It is also contemplated that the compounds of this invention will be effective in preventing relapse of obsessive-compulsive disorder.

The invention provides a method of treating obsessions and compulsions in a subject with
20 obsessive-compulsive disorder, which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's obsessions and compulsions.

It is contemplated that the compounds will be effective in treating panic disorder in
25 patients who have been diagnosed with panic disorder on the basis of frequency of occurrence of panic attacks, or by means of the CGI-Severity of Illness scale. It is further contemplated that the compounds described herein will be effective in inducing improvements in certain of the factors measured in these evaluations, such as a reduction in frequency or elimination of panic attacks an improvement in the CGI-Severity of
30 Illness scale or a CGI Global Improvement score of 1 (very much improved), 2 (much improved) or 3 (minimally improved). It is also contemplated that the compounds of this

invention will be effective in preventing relapse of panic disorder.

It is contemplated that the compounds will be effective in treating social anxiety disorder in patients who have been diagnosed as having social anxiety disorder based upon the administration of any of the following tests: the Liebowitz Social Anxiety Scale (LSAS), the CGI-Severity of Illness scale, the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), the axis V Social and occupational Functioning Assessment Scale of DSM-IV, the axis II (ICD10) World - Health organization Disability Assessment, Schedule 2 (DAS-2), the Sheehan Disability Scales, the Schneier Disability Profile, the World Health Organization Quality of Life-100 (WHOQOL-100)), or other tests as described in Ballenger, JC et al, 1998, J Clin Psychiatry 59 Suppl 17:54-60., which is incorporated herein by reference. It is further contemplated that the compounds described herein will be effective in inducing improvements as measured by these tests, such as the a change from baseline in the Liebowitz Social Anxiety Scale (LSAS), or a CGI-Global Improvement score of 1 (very much improved), 2 (much improved) or 3 (minimally improved). It is also contemplated that the compounds of this invention will be effective in preventing relapse of social anxiety disorder.

It is contemplated that the compounds will be effective in treating generalized anxiety disorder in patients who have been diagnosed as having this disorder based upon the diagnostic criteria described in DSM-IV. It is further contemplated that the compounds described herein will be effective in reducing symptoms of this disorder, such as the following: excessive worry and anxiety, difficulty controlling worry, restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, or sleep disturbance. It is also contemplated that the compounds of this invention will be effective in preventing relapse of general anxiety disorder.

It is contemplated that the compounds will be effective in treating PTSD in patients who have been diagnosed as having PTSD based upon the administration of any of the

following tests: Clinician-Administered PTSD Scale Part 2 (CAPS) and the patient-rated Impact of Event Scale (IES). It is further contemplated that the compounds described herein will be effective in inducing improvements in the scores of the CAPS, IES, CGI-Severity of Illness or CGI-Global Improvement tests. It is also contemplated that the
5 compounds of this invention will be effective in preventing relapse of PTSD.

The compounds described herein may be used to prevent, control or treat schizophrenia, paranoia or other related disorders of dopamine transmission.

10 The compounds can be administered in combination with anti-anxiety agents. Classes of anti-anxiety agents include: benzodiazepines (e.g. alprazolam (Xanax®), chlordiazepoxide (Librium®), clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam, and pharmaceutically acceptable salts thereof);
15 5-HT_{1A} agonist or antagonist, especially 5HT_{1A} partial agonists (e.g. the 5-HT_{1A} receptor partial agonists buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof); corticotropin releasing factor (CRF) antagonists (including those described in WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676, and WO 94/13677); phenothiazines (including promethazine, chlorpromazine, and trifluoperazine); monoamine oxidase inhibitors (MAOIs, e.g.
20 isocarboxazid (Marplan®), phenelzine (Nardil®), tranlycypromine (Parnate®) and selegiline, and pharmaceutically acceptable salts thereof); reversible inhibitors of monoamine oxidase (RIMAs, e.g. moclobemide and pharmaceutically acceptable salts thereof); tricyclic antidepressants (TCAs, e.g. amitriptyline (Elavil®), amoxapine, clomipramine, desipramine (Norpramin®), doxepin, imipramine (Tofranil®), maproline, nortriptyline (Aventyl® and Pamelor®), perphenazine, protriptyline, and trimipramine
25 (Surmentil®) and pharmaceutically acceptable salts thereof); atypical antidepressants including bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof; and selective serotonin reuptake inhibitors (SSRIs, e.g. paroxetine (Paxil®), venlafaxine, fluvoxamine, fluoxetine (Prozac®),
30 citalopram (Celexa®), escitalopram, and sertraline (Zoloft®) and pharmaceutically acceptable salts thereof).

The compounds can also be used in a co-therapy with a second agent that has analgesic activity. Analgesics which can be used in co-therapy include, but are not limited to: NSAIDs (e.g., acetaminophen, acetaminophen, acetyl salicylic acid, alclufenac,

- 5 alminoprofen, apazone, aspirin, benoxaprofen, bezpiperylon, bucloxic acid, carprofen, clidanac, diclofenac, diclofenac, diflunisal, diflusal, etodolac, fenbufen, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, flufenisal, fluprofen, flurbiprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketoprofen,
- 10 ketorolac, meclofenamic acid, meclofenamic acid, mefenamic acid, mefenamic acid, mioprofen, mofebutazone, nabumetone oxaprozin, naproxen, naproxen, niflumic acid, oxaprozin, oxpinac, oxyphenbutazone, phenacetin, phenylbutazone, phenylbutazone, piroxicam, piroxicam, pirprofen, pranoprofen, sudoxicam, tenoxicam, sulfasalazine, sulindac, sulindac, suprofen, tiaprofenic acid, tiopinac, tioprofen, tolifenamic acid,
- 15 tolmetin, tolmetin, zidometacin, zomepirac, and zomepirac), a non-narcotic analgesic such as tramadol, an opioid or narcotic analgesic (e.g., APF112, beta funaltrexamine, buprenorphine, butorphanol, codeine, cypridime, dezocine, dihydrocodeine, diphenyloxyate, enkephalin pentapeptide, fedotozine, fentanyl, hydrocodone, hydromorphone, levorphanol, loperamide, meperidine, mepivacaine, methadone, methyl
- 20 naloxone, morphine, nalbuphine, nalmeferene, naloxonazine, naloxone, naltrexone, naltrindole, nor-binaltorphimine, oxycodone, oxymorphone, pentazocine, propoxyphene, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033, SSR-241585), CCK receptor antagonists (e.g., loxiglumide), NK3 receptor antagonists (e.g., talnetant, osanetant SR-142801, SSR-241585), norepinephrine-serotonin reuptake
- 25 inhibitors (NSRI; e.g., milnacipran), vanilloid receptor agonists and antagonists, cannabinoid receptor agonists (e.g., arvanil), sialorphan, compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH₂; WO 01/019849 A1), Tyr-Arg (kyotorphin), CCK receptor agonists (e.g., caerulein), conotoxin peptides, peptide analogs of thymulin, dexloxiglumide (the R-isomer of loxiglumide; WO
- 30 88/05774), and analgesic peptides (e.g., endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance P).

In addition, certain antidepressants can be used in co-therapy either because they have analgesic activity or are otherwise beneficial to use in combination with an analgesic. Examples of such anti-depressants include: selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, sertraline), serotonin-norepinephrine dual uptake inhibitors, venlafaxine and nefazadone. Certain anti-convulsants have analgesic activity and are useful in co-therapy. Such anti-convulsants include: gabapentin, carbamazepine, phenytoin, valproate, clonazepam, topiramate and lamotrigine. Such agents are considered particularly useful for treatment of neuropathic pain, e.g., treatment of trigeminal neuralgia, postherpetic neuralgia, and painful diabetic neuropathy. Additional compounds useful in co-therapy include: alpha-2-adrenergic receptor agonists (e.g., tizanidine and clonidine), mexiletine, corticosteroids, compounds that block the NMDA (N-methyl-D-aspartate) receptor (e.g. dextromethorphan, ketamine, and amantadine), glycine antagonists, carisoprodol, cyclobenzaprine, various opiates, nonopioid antitussive (e.g. dextromethorphan, carmiphen, caramiphen and carbetapentane), opioid antitussives (e.g. codeine, hydrocodone, metaxolone. The compounds described herein can also be combined with inhalable gaseous nitric oxide (for treating pulmonary vasoconstriction or airway constriction), a thromboxane A2 receptor antagonist, a stimulant (i.e. caffeine), an H₂ -antagonist (e.g. ranitidine), an antacid (e.g. aluminum or magnesium hydroxide), an antiflatulent (e.g. simethicone), a decongestant (e.g. phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levodesoxyephedrine), a prostaglandin (e.g. misoprostol, enprostil, rioprostil, omoprostol or rosaprostol), a diuretic, a sedating or non-sedating histamine H₁ receptor antagonists/antihistamines (i.e. any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: - 4 astemizole, acrivastine, antazoline, astemizole, azatadine, azelastine, astemizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chlorpheniramine maleate, cimetidine, clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine succinate, doxylamine, ebastine, efletirizine, epinastine,

farnotidine, fexofenadine, hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norastemizole, noraztemizole, phenindamine, pheniramine, picumast, promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimeprazine, tripelenamine, and triprolidine; a 5HT1 agonist, such as a triptan (e.g. sumatriptan or naratriptan), an adenosine A1 agonist, an EP ligand, a sodium channel blocker (e.g. lamotrigine), a substance P antagonist (e.g. an NK antagonist), a cannabinoid, a 5-lipoxygenase inhibitor, a leukotriene receptor antagonist/leukotriene antagonists/LTD4 antagonists (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafirlukast, montelukast, montelukast sodium (Singulair®), pranlukast, iralukast, pobilukast, SKB-106,203 and compounds described as having LTD4 antagonizing activity described in US 5,565,473, a DMARD (e.g. methotrexate), a neurone stabilising antiepileptic drug, a mono-aminergic uptake inhibitor (e.g. venlafaxine), a matrix metalloproteinase inhibitor, a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor, an inhibitor of the release, or action, of tumor necrosis factor, an antibody therapy, such as a monoclonal antibody therapy, an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator (e.g. interferon), a local anaesthetic, a known FAAH inhibitor (e.g., PMSF, URB532, URB597, or BMS-1, as well as those described in those described in WO04033652, US6462054, US20030092734, US20020188009, US20030195226, and WO04033422), an antidepressant (e.g., VPI-013), a fatty acid amide (e.g. anandamide, N-palmitoyl ethanolamine, N-oleoyl ethanolamide, 2-arachidonoylglycerol, or oleamide), arvanil, analogs of anandamide and arvanil as described in US 20040122089, and a proton pump inhibitor (e.g., omeprazole, esomeprazole, lansoprazole, pantorazole and rabeprazole).

The compound described herein can also be used in a co-therapy with a second agent that is a cannabinoid receptor antagonist to prevent and/or treat obesity and other appetite related disorders.

Combinations for Co-Morbid Conditions

It will be appreciated by one skilled in the art that a therapy administered in combination with the compounds described herein can be directed to the same or a different disorder target as that being targeted by the compounds described herein.

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Administration of the compound described herein may be first, followed by the other therapy; or administration of the other therapy may be first or they may be administered simultaneously either in two separate compositions or combined in a single composition. The other therapy is any known in the art to treat, prevent, or reduce the symptoms of the targeted disorder, e.g., a sleep disorder, or other disorders, e.g., other CNS disorders. In addition, some embodiments of the present invention have compounds administered in combination with other known therapies for the target disorder. Furthermore, the other therapy includes any agent of benefit to the patient when administered in combination with the disclosed compound.

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For example, in some embodiments where the other therapy is a drug, it is administered as a separate formulation or in the same formulation as the compound described herein. A compound described herein is administered in combination therapy with any one or more of commercially-available, over-the-counter or prescription medications, including, but not limited to antimicrobial agents, fungistatic agents, germicidal agents, hormones, antipyretic agents, antidiabetic agents, bronchodilators, antidiarrheal agents, antiarrhythmic agents, coronary dilation agents, glycosides, spasmolytics, antihypertensive agents, antidepressants, antianxiety agents, other psychotherapeutic agents, corticosteroids, analgesics, contraceptives, nonsteroidal anti-inflammatory drugs, blood glucose lowering agents, cholesterol lowering agents, anticonvulsant agents, other antiepileptic agents, immunomodulators, anticholinergics, sympatholytics, sympathomimetics, vasodilatory agents, anticoagulants, antiarrhythmics, prostaglandins having various pharmacologic activities, diuretics, sleep aids, antihistaminic agents, antineoplastic agents, oncolytic agents, antiandrogens, antimalarial agents, antileprosy agents, and various other types of drugs. See Goodman and Gilman's The Basis of

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Therapeutics (Eighth Edition, Pergamon Press, Inc., USA, 1990) and The Merck Index (Eleventh Edition, Merck & Co., Inc., USA, 1989).

Combinations useful in treatment of diabetes

5 Suitable agents of use in combination with a compound described herein include anti-diabetic agents such as (1) PPAR γ agonists such as glitazones (e.g., ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone; rosiglitazone; troglitazone; BRL49653; CLX-0921; 5-BTZD, and GW-0207, LG-100641, and LY-300512, and the like and compounds disclosed in PCT publication Nos. W097/10813,
10 W097/27857, W097/28115, W097/28137, W097/27847, W003/000685, W003/027112, W003/035602, W003/048130, W003/055867, and the like; (2) biguanides such as buformin; metformin; and phenformin, and the like; (3) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, such as ISIS 113715, and those disclosed in W003/032916, W003/032982, W003/041729, W003/055883; (4) sulfonylureas such as acetohexamide;
15 carbutamide; chlorpropamide; diabinese; glibenclamide; glipizide; glyburide (glibenclamide); glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide, and the like; (5) meglitinides such as repaglinide, and nateglinide, and the like; (6) alpha glucoside hydrolase inhibitors such as acarbose; adiposine; camiglibose; emiglitate; miglitol; voglibose; pradimicin-Q; salbostatin; CKD-711; MDL-
20 25,637; MDL-73,945; and MOR 14, and the like; (7) alpha-amylase inhibitors such as tendamistat, trestatin, and A1-3688, and the like; (8) insulin secretagogues such as linogiride; and A-4166, and the like; (9) fatty acid oxidation inhibitors, such as clomoxir, and etomoxir, and the like; (10) A2 antagonists, such as midaglizole; isaglidole; deriglidole; idazoxan; eaoxan; and fluparoxan, and the like; (11) insulin or insulin
25 mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (73-7) (insulintropin); and GLP-1 (7-36)-NH₂, and the like; (12) non-thiazolidinediones such as JT-501, and farglitazar (GW-2570/GI-262579), and the like; (13) PPAR α/γ dual
agonists such as BVT-142, CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-
30 796449, LR-90, MK-0767, SB 219994, muraglitazar and reglitazar (JTT-501) and those disclosed in W099/16758, W099/19313, W099/20614, W099/38850, W000/23415,

WO00/23417, WO00/23445, WO00/50414, WO01/00579, WO01/79150,
WO02/062799, WO03/004458, WO03/016265, WO03/018010, WO03/033481,
WO03/033450, WO03/033453, WO03/043985, WO 031053976; and (14) other insulin
sensitizing drugs; (15) VPAC2 receptor agonists; (16) GLK modulators, such as those
5 disclosed in WO03/015774; (17) retinoid modulators such as those disclosed in
WO03/000249; (18) GSK 3 β /GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-
fluorophenyl)-1H-imidazol-5-yl]pyridine and those compounds disclosed in
WO03/024447, WO03/037869, WO03/037877, WO03/037891, WO03/068773, EP
1295884, EP 1295885, and the like; (19) glycogen phosphorylase (HGLPa) inhibitors,
10 such as those disclosed in WO03/037864; (20) ATP consumption promoters such as
those disclosed in WO03/007990; (21) TRB3 inhibitors, (22) vanilloid receptor ligands
such as those disclosed in WO03/049702, (23) hypoglycemic agents such as those
disclosed in WO03/015781, WO03/040114, (24) glycogen synthase kinase 3 inhibitors
such as those disclosed in WO03/035663, (25) and agents such as those disclosed in
15 WO99/51225 and US 20030134890; and WO01/24786, WO03/059870; (26) Insulin-
responsive DNA binding protein-1 (IRDBP-1) as disclosed in WO03/057827, and the
like; (27) Adenosine A2 antagonists such as those disclosed in WO03/035639,
WO03/035640, and the like.

20 Combinations Useful in Treatment of Hyperlipidemia

Suitable agents of use in combination with a compound described herein include lipid
lowering agents such as:

(1) bile acid sequestrants such as, cholestyramine, colesevelam, colestipol,
dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid®; LoCholest®; and
25 Questran®, and the like; (2) HMG-CoA reductase inhibitors such as atorvastatin,
bervastatin, carvastatin, cerivastatin, crilvastatin, dalvastatin, fluvastatin, glenvastatin,
itavastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rivastatin, rosuvastatin,
simvastatin, sirrivastatin, and ZD-4522, and the like and compounds disclosed in
WO03/033481; (3) HMG-CoA synthase inhibitors; (4) cholesterol absorption inhibitors
30 such as stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones
such as ezetimibe, and the like; (5) acyl coenzyme A -cholesterol acyl transferase

(ACAT) inhibitors such as avasimibe (Current Opinion in Investigational Drugs. 3(9):291-297 (2003)), eflucimibe, KY505, SMP 797, CL-277,082 (Clin Pharmacol Ther. 48(2):189-94 (1990)) and the like; (6) CETP inhibitors such as JTT 705 identified as in Nature. 406, (6792):203-7 (2000), torcetrapib (CP-529,414 described in US20030186952 and WO2000017164), CP 532,632, BAY63-2149, SC 591, SC 795, and the like including those described in Current Opinion in Investigational Drugs. 4(3):291-297 (2003). (7) squalene synthetase inhibitors; (8) antioxidants such as probucol, AGI-1067 and the like; (9) PPAR α agonists such as bezafibrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, etofibrate, fenofibrate, gemcabene, and gemfibrozil, lifibrol, GW 7647, BM 170744, LY518674; and other fibric acid derivatives, such as Atromid®, Lopid® and Tricor®, and those disclosed in WO03/033456, WO03/033481, WO03/043997, WO03/048116, WO03/053974, WO03/059864, WO03/05875, and the like; (10) FXR receptor modulators such as GW 4064, SR 103912, and the like; (11) LXR receptor modulators such as GW 3965, T9013137, and XTC0179628, and those disclosed in US20030125357, WO03/045382, WO03/053352, WO03/059874, and the like; (12) lipoprotein synthesis inhibitors such as niacin; (13) renin angiotensin system inhibitors; (14) PPAR δ partial agonists, such as those disclosed in WO03/024395; (15) bile acid reabsorption inhibitors, such as BARI 1453, SC435, PHA384640, S8921, AZD7706, and the like; (16) PPAR δ agonists such as GW 501516, and GW 590735, and the like, such as those disclosed in W097/28149, WO01/79197, WO02/14291, WO02/46154, WO02/46176, WO02/076957, WO03/016291, WO03/033493; (17) triglyceride synthesis inhibitors; (18) microsomal triglyceride transport (MTTP) inhibitors, such as inplitapide, LAB687, and CP346086, and the like; (19) transcription modulators; (20) squalene epoxidase inhibitors; (21) low density lipoprotein (LDL) receptor inducers; (22) platelet aggregation inhibitors; (23) 5-LO or FLAP inhibitors; and (24) niacin receptor agonists; (25) PPAR modulators such as those disclosed in WO99/07357, WO99/11255, WO99/12534, WO99/15520, WO99/46232, WO00/12491, WO00/23442, WO00/236331, WO00/236332, WO00/218355, WO00/238553, WO01/25181, WO01/79150, WO02/79162, WO02/100403, WO02/102780, WO02/081428, WO03/016265, WO03/033453, WO03/042194, WO03/043997, WO03/066581, and the like; (26) niacin-bound chromium, as disclosed in WO03/039535;

(27) substituted acid derivatives disclosed in WO03/040114; (28) apolipoprotein B inhibitors such as those disclosed in WO02/090347, WO02/28835, WO03/045921, WO03/047575; (29) Factor Xa modulators such as those disclosed in WO03/047517, WO03/047520, WO03/048081

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Combinations useful in treatment of Hypertension

Suitable agents of use in combination with a compound described herein include anti-hypertensive agents such as:

- (1) diuretics, such as thiazides, including chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, and hydrochlorothiazide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide, and torsemide; potassium sparing agents, such as amiloride, and triamterene; and aldosterone antagonists, such as spironolactone, eplerenone, and the like; (2) beta-adrenergic blockers such as acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efondipine, felodipine, gallopamil, isradipine, lacidipine, lemdipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and the like; (4) angiotensin converting enzyme (ACE) inhibitors such as benazepril; captopril; ceranapril; cilazapril; delapril; enalapril; enalapril; fosinopril; imidapril; lisinopril; losinopril; moexipril; quinapril; quinaprilat; ramipril; perindopril; perindopril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as omapatrilat, cadoxatril and ccadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotinyl alcohol, and the like; (8) angiotensin II receptor antagonists such as aprosartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, prazosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K, and RNH6270, and the like; (9) α/β adrenergic blockers such as nipradilol, arotinolol and amosulalol, and the like; (10) alpha

1 blockers, such as terazosin, urapidil, prazosin, bunazosin, trimazosin, doxazosin,
naftopidil, indoramin, WHP 164, and XEN010, and the like; (11) alpha 2 agonists such as
lofexidine, tiamenidine, moxonidine, rilmenidine and guanobenz, and the like; (12)
aldosterone inhibitors, and the like; and (13) angiopoietin-2-binding agents such as those
5 disclosed in WO03/030833.

Cox and FAAH related therapeutic methods

The compounds can be used, for example, to treat conditions or disorders in which it is
10 considered desirable to reduce or eliminate COX-2 activity and/or FAAH activity and/or
MAGL. Thus, they can be used in any situation in which a COX-2 inhibitor or FAAH
inhibitor or MAGL inhibitor is used as well as in other situations. For example,
compounds and related prodrugs can be used to treat an inflammatory disorder, including
both disorders in which inflammation is considered a significant component of the
15 disorder and those in which inflammation is considered a relatively minor component of
the disorder, to treat acute and chronic pain (analgesic) and to treat fever (antipyretic).
Among the inflammatory disorders that can be treated are auto-immune disorders.

Disorders that can be treated include: arthritis (including rheumatoid arthritis,
20 spondyloarthropathies, gouty arthritis, degenerative joint diseases (i.e. osteoarthritis),
systemic lupus erythematosus, ankylosing spondylitis, acute painful shoulder, psoriatic,
and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis,
bursitis, skin inflammation disorders (i.e. psoriasis, eczema, burns, dermatitis), enuresis,
eosinophilic disease, gastrointestinal disorders (including inflammatory bowel disease,
25 peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, Crohn's disease,
gastritis, irritable bowel syndrome and ulcerative colitis), and disorders ameliorated by a
gastroprokinetic agent (i.e. ileus, for example post-operative ileus and ileus during sepsis;
gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic
esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food
30 allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD)
and non-cardiac chest pain (NCCP)).

The compounds can also be used in the treatment of symptoms associated with influenza or other viral infections, common cold, sprains and strains, myositis, neuralgia, synovitis, injuries such as sports injuries and those following surgical and dental procedures, coagulation disorders, kidney disease (e.g., impaired renal function), ophthalmic disorders (including glaucoma, retinitis, retinopathies, uveitis and acute injury to the eye tissue), liver diseases (i.e., inflammatory liver disease including chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis and liver transplant rejection), and pulmonary inflammatory diseases (e.g., including asthma, allergic rhinitis, respiratory distress syndrome chronic bronchitis, and emphysema). Compositions comprising a compound described herein and related prodrugs thereof can also be used to treat, for example, inflammation associated with: vascular diseases, migraine headaches, tension headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, multiple sclerosis, and ischemia (e.g., myocardial ischemia), and the like. The compounds may be useful for treating neuroinflammation associated with brain disorders (e.g., Parkinson's disease and Alzheimer's disease) and chronic inflammation associated with cranial radiation injury. The compounds may be useful for treating acute inflammatory conditions (such as those resulting from infection) and chronic inflammatory conditions (such as those resulting from asthma, arthritis and inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds can also be administered to those prior to surgery or taking anticoagulants. The compounds may reduce the risk of a thrombotic cardiovascular event which is defined as any sudden event of a type known to be caused by platelet aggregation, thrombosis, and subsequent ischemic clinical events, including thrombotic or thromboembolic stroke, myocardial ischemia, myocardial infarction, angina pectoris, transient ischemic attack (TIA; amaurosis fugax), reversible ischemic neurologic deficits, and any similar thrombotic event in any vascular bed (splanchnic, renal, aortic, peripheral, etc.).

The compounds may inhibit uterus contraction caused by hormones and prostanoid-induced smooth muscle contraction. The compounds may be useful in treating premature labor, menstrual cramps, menstrual irregularity, and dysmenorrhea.

- 5 The compounds described herein may inhibit cellular neoplastic transformations and metastatic tumor growth. The compounds described herein may be associated with reducing the number of adenomatous colorectal polyps. Thus, compounds and prodrugs may also be useful in reducing the risk of certain cancers, e.g., solid tumor cancers such as colon or colorectal cancer. The compounds and prodrugs may also be used in the
- 10 treatment of prevention of all cancers including cancers of the bladder, cancers associated with overexpression of HER-2/neu cervix, skin, esophagus, head and neck, lung including non small-cell lung cancers, kidney, pancreas, prostate, gall bladder and bile duct and endometrial cancers, gastric cancers, gliomas, hepatocellular carcinomas, colonic adenomas, mammary cancers, ovarian cancers and salivary cancers. In addition,
- 15 the compounds and prodrugs may be useful in treating large intestine cancer and prostate cancer. The compounds may also be useful in cases where the patient is at risk for cancer including oral premalignant lesions, cervical intraepithelial neoplasia, chronic hepatitis, bile duct hyperplasia, atypical adenomatous hyperplasia of lung, prostatic, intraepithelial neoplasia, bladder dysplasia, actinic keratoses of skin, colorectal adenomas, gastric
- 20 metaplasia, and Barrett's esophagus.

- Compounds described herein are also useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease (and precursors thereof), Pick's disease, Huntington's chorea, Parkinson's disease
- 25 and Creutzfeldt-Jakob disease), and vascular dementia (including multiinfarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

- 30 Compounds may also prevent neuronal injury by inhibiting the generation of neuronal free radicals (and hence oxidative stress) and therefore are of use in the treatment of

stroke; epilepsy; and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures). The compounds may be useful to control or suppress seizures (including those that are chemically induced).

- 5 The compounds can be used in treatment of all varieties of pain including pain associated with a cough condition, pain associated with cancer, preoperative pain, arthritic pain and other forms of chronic pain such as post-operative pain, lumbosacral pain, musculo-skeletal pain, headache, migraine, muscle ache, lower back and neck pain, toothache and the like. The compounds are also useful for the treatment of neuropathic pain.
- 10 Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy;
- 15 sciatica; back pain, non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; pain related to chronic alcoholism, hypothyroidism, uremia, or vitamin deficiencies; pain related to compression of the nerves (e.g., Carpal Tunnel Syndrome), and pain resulting from physical trauma, amputation/phantom limb pain, cancer, toxins or
- 20 chronic inflammatory conditions. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation
- 25 (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).
- 30 The compounds may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic

retinopathy and tumor angiogenesis. The compounds may be used to inhibit angiogenesis, such as occurs in wet macular degeneration.

5 The compounds may also be used for treating sexual behavior problems and/or improving sexual performances.

Certain compounds are useful in the prevention and/or treatment of pain, in particular acute or chronic neurogenic pain, migraine, neuropathic pains including the forms associated with herpes virus and diabetes, acute or chronic pain associated with the
10 inflammatory diseases: arthritis, rheumatoid arthritis, osteoarthritis, spondylitis, gout, vascularitis, Crohn's disease, irritable bowel syndrome and acute/sharp or chronic pains at the periphery. The compounds can also be used to prevent and/or treat emesis, dizziness, vomiting, and nausea, especially after chemotherapy, food behavioral problems/feeding disorders (i.e. eating disorders, in particular anorexias and cachexias of
15 various natures, weight loss associated with cancer and other wasting conditions, or bulimia), neurological pathologies, psychiatric tremors (e.g., dyskinesias, dystonia, spasticity, obsessive compulsive behavior, Tourette's syndrome, all forms of depression and anxiety of any nature and origin, mood disturbances, psychoses), acute or chronic neurodegenerative diseases (e.g., Parkinson's disease, Alzheimer's disease, senile
20 insanity, Huntington's chorea, lesions related to cerebral ischemia and cranial and medullary traumas, epilepsy, sleep disorders (sleep apnea), cardiovascular diseases (in particular hypertension, cardiac arrhythmias, arteriosclerosis, heart attacks, cardiac ischemias, renal ischemia), cancers (benign tumors of the skin, papillomas and cerebral tumors, prostate tumors, cerebral tumors (glioblastomas, medullary epitheliomas,
25 medullary blastomas, neuroblastomas, tumors of origin, astrocytomas, astroblastomas, ependymomas, oligodendrogliomas, plexus tumor, neuroepithelioma, epiphysis tumor, ependyblastomas, malignant meningiomas, sarcomatosis, malignant melanomas, schwan cell cancers), disorders of the immune system (in particular autoimmune diseases including psoriasis, erythematous lupus), diseases of conjunctive or connective tissue,
30 Sjogren's syndrome, spondylarthritis ankylosis, undifferentiated spondylarthritis undifferentiated, Behcet's disease, autoimmune hemolytic anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amyloses, graft rejection, and illnesses affecting the

blastocytes, allergic diseases (i.e., immediate or delayed hypersensitivity, allergic rhinitis or conjunctivitis, contact dermatitis), viral or bacterial parasitic infectious diseases (i.e. AIDS, meningitis), inflammatory diseases (in particular arthritic diseases: arthritis, rheumatoid arthritis osteoarthritis, spondylitis, gout, vascularitis, Crohn's disease, irritable bowel syndrome, osteoporosis, psoriasis, ocular infections and disorders (i.e. ocular hypertension, glaucoma, wet macular degeneration), lung diseases (i.e. diseases of the respiratory tracts, bronchospasms, cough, asthma, chronic bronchitis, chronic obstruction of the respiratory tracts, emphysema), gastrointestinal disorders(i.e. irritable bowel syndrome, intestinal inflammatory disorders, ulcers, diarrheas, acid reflux), urinary incontinence, vesical inflammation, movement disorders, psychomotor disorders, hypertension, and AIDS-related complex. The compounds can be used as a sleep aid, to treat insomnia or to induce sleep. The compounds may be used to reduce or control body weight (or fat) or prevent and/or treat obesity or other appetite related disorders related to the excess consumption of food, ethanol and other appetizing substances. The compounds may be used to modulate lipid metabolism, reduce body fat (e.g., via increasing fat utilization) or reduce (or suppress) appetite (e.g., via inducing satiety). The compounds may be used to prevent, control or treat schizophrenia, paranoia or other related disorders, or other disorders of dopamine transmission.

The compounds can also be used to treat anxiety (including generalized anxiety disorder, panic disorder, and social anxiety Disorder) and depression.

The compounds (for example, FAAH inhibitors) can also be used in the treatment of pollakiuria, for example in the treatment of urinary incontinence, uresiesthesia urgency, or overactive bladder. Pollakiuria refers to the condition characterized by the voiding or passing of small quantities of urine more frequently than normal. Interstitial cystitis, chronic prostatitis, neuropathy (for example, resulting from neurogenic bladder or cerebral infarction), lower urinary tract prostatic hypertrophy, and aging, are among the conditions associated with pollakiuria.

CRTH2 related therapeutic methods

The compounds described herein that are CRTH2 antagonists can be used, for example,
5 to prevent and/or treat conditions or disorders in which it is considered desirable to
reduce or eliminate CRTH2 activity. The compounds described herein that are CRTH2
agonists can be used, for example, to prevent and/or treat conditions in which it is
considered desirable to: (1) downregulate CRTH2 activity via desensitization; (2)
10 downregulate non-CRTH2 chemokine receptor activity via cross-desensitization or (3)
shift the balance of Th1 and Th2 cells towards Th2 via agonism at CRTH2. CRTH2
agonists are expected to be especially useful in the prevention and/or treatment of disease
and disorders characterized by an imbalance of Th1/Th2 that is shifted towards Th1 cells,
e.g., rheumatoid arthritis, Type I diabetes, psoriasis, gastritis, irritable bowel syndrome,
multiple sclerosis, painless thyroiditis, lupus, and Crohn's Disease.

15 Compounds that are CRTH2 antagonists or agonists may be used to aid in preventing
and/or treating a disease or disorder mediated, regulated or influenced by, for example,
Th2 cells, eosinophils, basophils, platelets, Langerhans cells, dendritic cells or mast cells.
They also may be used to aid in the prevention or treatment of a disease or disorder
20 mediated, regulated or influenced by PGD₂ and metabolites thereof, such as 13,14-
dihydro-15-keto-PGD₂ and 15-deoxy-Δ^{12,14}-PGD₂.

CRTH2 antagonists are expected to be useful in the prevention and/or treatment of
disease and disorders characterized by undesirable activation of Th2 cells, eosinophils,
25 and basophils e.g., asthma, atopic dermatitis, allergic rhinitis, allergies (e.g., food
allergies, dust allergies, pollen allergies, mold allergies), and Grave's Disease.

Compounds that are CRTH2 antagonists or agonists (and similarly, compounds that are
DP-1 agonists or antagonists) may be used to aid in preventing and/or treating the
30 following types of diseases, conditions and disorders:

respiratory tract/obstructive airways diseases and disorders including: rhinorrhea, tracheal constriction, airway contraction, acute-, allergic, atrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and

5 pseudomembranous rhinitis), serofulous rhinitis, perennial allergic rhinitis, seasonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis), , asthma (such as bronchial, allergic, intrinsic, extrinsic, exercise-induced, cold air-induced, occupational, bacterial infection-induced, and dust asthma particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness)), bronchitis (including chronic,
10 acute, arachidic, catarrhal, croupus, phthinoid and eosinophilic bronchitis), pneumoconiosis, chronic inflammatory diseases of the lung which result in interstitial fibrosis, such as interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, or other autoimmune conditions), acute lung injury (ALI) , adult respiratory distress syndrome (ARDS), chronic obstructive
15 pulmonary, airways or lung disease (CORD, COAD, COLD or COPD, such as irreversible COPD), chronic sinusitis, conjunctivitis (e.g. allergic conjunctivitis), cystic fibrosis, extrinsic allergic alveolitis (like farmer's lung and related diseases), fibroid lung, hypersensitivity lung diseases, hypersensitivity pneumonitis, idiopathic interstitial pneumonia, nasal congestion, nasal polyposis, otitis media, and cough (chronic cough
20 associated with inflammation or iatrogenic induced), pleurisy, pulmonary congestion, emphysema, bronchiectasis, sarcoidosis, lung fibrosis, including cryptogenic fibrosing alveolitis, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections, vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension, acute viral infection
25 including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies, and food related allergies which may have effects
30 remote from the gut (such as migraine, rhinitis and eczema);

bone and joint related diseases and disorders including: osteoporosis, arthritis (including rheumatic, infectious, autoimmune), seronegative spondyloarthropathies (such as ankylosing spondylitis, rheumatoid spondylitis, psoriatic arthritis, enthesopathy, Bechet's disease, Marie-Strumpell arthritis, arthritis of inflammatory bowel disease, and
5 Reiter's disease), systemic sclerosis, osteoarthritis/osteoarthrosis, both primary and secondary to e.g. congenital hip dysplasia, cervical and lumbar spondylitis, and low back and neck pain, Still's disease, reactive arthritis and undifferentiated spondarthropathy, septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Pott's disease and Poncet's syndrome, acute and chronic crystal-
10 induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursar and synovial inflammation, primary and secondary Sjogren's syndrome, systemic sclerosis and limited scleroderma, mixed connective tissue disease, and undifferentiated connective tissue disease, inflammatory myopathies including, polymyalgia rheumatica, juvenile arthritis including idiopathic inflammatory
15 arthritides of whatever joint distribution and associated syndromes, other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), rheumatic fever and its systemic complications, vasculitides including giant cell arteritis, Takayasu's arteritis, polyarteritis nodosa, microscopic polyarteritis, and vasculitides to associated with viral infection, hypersensitivity reactions, cryoglobulins, paraproteins,
20 low back pain, Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease, drug-induced arthralgias, tendonitides, polychondritis, and myopathies;

skin and eye related diseases and disorders including: glaucoma, ocular hypertension,
25 cataract, retinal detachment, psoriasis, xeroderma, eczematous diseases (like atopic dermatitis, contact dermatitis, and seborrheic dermatitis), phytodermatitis, photodermatitis, cutaneous eosinophilias, chronic skin ulcers, cutaneous lupus erythematosus, contact hypersensitivity/allergic contact dermatitis (including sensitivity to poison ivy, sumac, or oak), and eosinophilic folliculitis (Ofuji's disease), pruritus, drug
30 eruptions, urticaria (acute or chronic, allergic or non-allergic), acne, erythema, dermatitis herpetiformis, scleroderma, vitiligo, lichen planus, lichen sclerosus et atrophica,

pyodermma gangrenosum, skin sarcoid, pemphigus, pemphigoid, epidermolysis bullosa, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Stevens-Johnson syndrome, Weber-Christian syndrome, erythema multiforme, cellulitis, both, infective and non infective, panniculitis, cutaneous Lymphomas, non-melanoma skin cancer and other dysplastic lesions, blepharitis, iritis, anterior and posterior uveitis, choroiditis, autoimmune, degenerative or inflammatory disorders affecting the retina, ophthalmitis including sympathetic ophthalmitis, sarcoidosis, xerosis (for example as described in US2005192357A1) infections including viral, fungal, and bacterial;

gastrointestinal tract and abdominal related diseases and disorders including: Celiac/coeliac disease (e.g. celiac sprue), cholecystitis, enteritis (including eosinophilic gastroenteritis), eosinophilic esophagitis, eosinophilic gastrointestinal inflammation, allergen induced diarrhea, enteropathy associated with seronegative arthropathies, gastritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), colitis, irritable bowel syndrome, glossitis, gingivitis, periodontitis, oesophagitis, including reflux, proctitis, fibrosis and cirrhosis of the liver, pancreatitis, both acute and chronic, hepatitis (alcoholic, steatohepatitis and chronic viral), and gastrointestinal related allergic disorders;

hematological disorders including: anemias, myeloproliferative disorders, hemorrhagic disorders, leukopenia, eosinophilic disorders, leukemias, lymphomas, plasma cell dyscrasias, disorders of the spleen;

metabolic disorders including, but not limited to: obesity, amyloidosis, disturbances of the amino acid metabolism like branched chain disease, hyperaminoacidemia, hyperaminoaciduria, disturbances of the metabolism of urea, hyperammonemia, mucopolysaccharidoses e.g. Maroteaux-Lamy syndrom, storage diseases like glycogen storage diseases and lipid storage diseases, glycogenosis I diseases like Cori's disease, malabsorption diseases like intestinal carbohydrate malabsorption, oligosaccharidase deficiency like maltase-, lactase-, sucrase-insufficiency, disorders of the metabolism of

fructose, disorders of the metabolism of galactose, galactosaemia, disturbances of carbohydrate utilization like diabetes, hypoglycemia, disturbances of pyruvate metabolism, hypolipidemia, hypolipoproteinemia, hyperlipidemia, hyperlipoproteinemia, carnitine or carnitine acyltransferase deficiency, disturbances of the porphyrin

5 metabolism, porphyrins, disturbances of the purine metabolism, lysosomal diseases, metabolic diseases of nerves and nervous systems like gangliosidoses, sphingolipidoses, sulfatidoses, leucodystrophies, Lesch- Nyhan syndrome; osteoporosis, osteomalacia like osteoporosis, osteopenia, osteogenesis imperfecta, osteopetrosis, osteonecrosis, Paget's disease of bone, hypophosphatemia; cerebellar dysfunction, disturbances of brain

10 metabolism like dementia, Alzheimer's disease, Huntington's chorea, Parkinson's disease, Pick's disease, toxic encephalopathy, demyelinating neuropathies like inflammatory neuropathy, Guillain-Barre syndrome; primary and secondary metabolic disorders associated with hormonal defects like any disorder stemming from either an

15 hyperfunction or hypofunction of some hormone-secreting endocrine gland and any combination thereof, Sipple's syndrome, pituitary gland dysfunction and its effects on other endocrine glands, such as the thyroid, adrenals, ovaries, and testes, acromegaly, hyper- and hypothyroidism, euthyroid goiter, euthyroid sick syndrome, thyroiditis, and thyroid cancer, over or underproduction of the adrenal steroid hormones, adrenogenital syndrome, Cushing's syndrome, Addison's disease of the adrenal cortex, Addison's

20 pernicious anemia, primary and secondary aldosteronism, diabetes insipidus, diabetes mellitus, carcinoid syndrome, disturbances caused by the dysfunction of the parathyroid glands, pancreatic islet cell dysfunction, diabetes, disturbances of the endocrine system of the female like estrogen deficiency, resistant ovary syndrome; muscle weakness, myotonia, Duchenne's and other muscular dystrophies, dystrophia myotonica of Steinert,

25 mitochondrial myopathies like I disturbances of the catabolic metabolism in the muscle, carbohydrate and lipid storage myopathies, glycogenoses, myoglobinuria, malignant hyperthermia, polymyalgia rheumatica, dermatomyositis, primary myocardial disease, cardiomyopathy; disorders of the ectoderm, neurofibromatosis, scleroderma and polyarthritis, Louis-Bar syndrome, von Hippel-Lindau disease, Sturge-Weber syndrome,

30 tuberous sclerosis, amyloidosis, porphyria; sexual dysfunction of the male and female; confused states and seizures due to inappropriate secretion of antidiuretic hormone from

the pituitary gland, Liddle's syndrome, Bartter's syndrome, Fanconi's I syndrome, and renal electrolyte wasting;

transplant rejection related conditions including: acute and chronic allograft rejection

5 following solid organ transplant, for example, transplantation of kidney, heart, liver, lung, and cornea, chronic graft versus host disease, skin graft rejection, and bone marrow transplant rejection;

genitourinary related conditions including nephritis (interstitial, acute interstitial

10 (allergic), and glomerulonephritis), nephrotic syndrome, cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer, acute and chronic urethritis, prostatitis, epididymitis, oophoritis, salpingitis, vulvo vaginitis, Peyronie's disease, and erectile dysfunction;

15 CNS related diseases and disorders including, but not limited to: neurodegenerative diseases, Alzheimer's disease and other cementing disorders including CJD and nvCJD, amyloidosis, and other demyelinating syndromes, cerebral atherosclerosis and vasculitis, temporal arteritis, myasthenia gravis, acute and chronic so pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache,
20 migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies, neurosarcoidosis, to brain injuries, cerebrovascular diseases and their consequences, Parkinson's disease, corticobasal degeneration, motor neuron disease, dementia, including ALS (Amyotrophic lateral
25 sclerosis), multiple sclerosis, traumatic brain injury, stroke, post-stroke, post-traumatic brain injury, and small-vessel cerebrovascular disease, dementias, vascular dementia, dementia with Lewy bodies, frontotemporal dementia and Parkinsonism linked 1 to chromosome 17, frontotemporal dementias, including Pick's disease, progressive nuclear palsy, corticobasal degeneration, Huntington's disease, thalamic degeneration, HIV
30 dementia, schizophrenia with dementia, and Korsakoff's psychosis, within the meaning of

the definition are also considered to be CNS disorders central and peripheral nervous system complications of malignant, infectious or autoimmune processes;

inflammatory or immunological diseases or disorders including: general inflammation (of
5 the nasal, pulmonary, and gastrointestinal passages), mastocytosis/mast cell disorders
(cutaneous, systemic, mast cell activation syndrome, and pediatric mast cell diseases),
mastitis (mammary gland), vaginitis, vasculitis (e.g., necrotizing, cutaneous, and
hypersensitivity vasculitis), Wegener granulomatosis, myositis (including polymyositis,
dermatomyositis), basophil related diseases including basophilic leukemia and basophilic
10 leukocytosis, and eosinophil related diseases such as Churg-Strauss syndrome,
eosinophilic granuloma, lupus erythematosus (such as, systemic lupus erythematosus,
subacute cutaneous lupus erythematosus, and discoid lupus erythematosus), Hashimoto's
thyroiditis, Grave's disease, type I diabetes, complications arising from diabetes mellitus,
other immune disorders, eosinophilia fasciitis, hyper IgE syndrome, Addison's disease,
15 antiphospholipid syndrome, acquired immune deficiency syndrome (AIDS), leprosy,
Sezary syndrome, paraneoplastic syndromes, and other autoimmune disorders, many of
which are named within;

cardiovascular diseases and disorders including: congestive heart failure, myocardial
20 infarction, ischemic diseases of the heart, all kinds of atrial and ventricular arrhythmias,
hypertension, cerebral trauma, occlusive vascular disease, stroke, cerebrovascular
disorder, atherosclerosis, restenosis, affecting the coronary and peripheral circulation,
pericarditis, myocarditis, inflammatory and auto-immune cardiomyopathies including
myocardial sarcoid, endocarditis, valvulitis, and aortitis including infective (e.g.
25 syphilitic), hypertensive vascular diseases, peripheral vascular diseases, and
atherosclerosis, vasculitides, disorders of the proximal and peripheral veins including
phlebitis and thrombosis, including deep vein thrombosis and complications of varicose
veins;

30 oncological diseases and disorders including: common cancers (prostate, breast, lung,
ovarian, pancreatic, bowel and colon, abdomen, stomach (and any other digestive system
cancers), liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary,

testicles, ovary, thymus, thyroid), eye, head, neck, nervous system (central and peripheral), lymphatic system, pelvic, skin, bone, soft tissue, spleen, thoracic, urogenital, and brain tumors), malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's Lymphoma, metastatic disease and tumour recurrences, and paraneoplastic syndromes, as well as hypergammaglobulinemia, lymphoproliferative diseases, disorders, and/or conditions, paraproteinemias, purpura (including idiopathic thrombocytopenic purpura), Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease; and

other diseases and disorders including: pain, migraine, sleep disorders, fever, sepsis, idiopathic thrombocytopenia pupura, post-operative adhesions, flushing, ischemic/reperfusion injury in the heart, brain, peripheral limbs, infection, viral infection, thrombosis, shock, septic shock, thermal regulation including fever, Raynaud's disease, gangrene, diseases requiring anti-coagulation therapy, congestive heart failure, mucus secretion disorders, pulmonary hypotension, prostanoid-induced smooth muscle contraction associated with dysmenorrhea and premature labor.

Compounds that are CRTH2 antagonists or agonists (and similarly, compounds that are DP-1 agonists or antagonists) may also be used to reduce hair (e.g. mammalian) growth as described in US20050112075A1.

Compounds that are CRTH2 agonists may be used as eating promoters and compounds that are CRTH2 antagonists may be used as eating inhibitors as described in WO2004030674.

Compounds that are modulators of CRTH2 are useful for the treatment of pain. Pain can also considered to be a CNS disorder. Pain can be associated with CNS disorders, such as multiple sclerosis, spinal cord injury, sciatica, failed back surgery syndrome, traumatic brain injury, epilepsy, Parkinson's disease, post- stroke, and vascular lesions in the brain and spinal cord (e.g., infarct, hemorrhage, vascular malformation). Non-central

neuropathic pain includes that associated with post mastectomy pain, phantom feeling, reflex sympathetic dystrophy (RSD), trigeminal neuralgia, radioculopathy, post-surgical pain, HIV/AIDS related pain, cancer pain, metabolic neuropathies (e.g., diabetic neuropathy, vasculitic neuropathy secondary to connective tissue disease), paraneoplastic polyneuropathy associated, for example, with carcinoma of lung, or leukemia, or lymphoma, or carcinoma of prostate, colon or stomach, trigeminal neuralgia, cranial neuralgias, and post-herpetic neuralgia. Pain associated with peripheral nerve damage, central pain (i.e. due to cerebral ischemia) and various chronic pain i.e., lumbago, back pain (low back pain), inflammatory and/or rheumatic pain. Headache pain (for example, migraine with aura, migraine without aura, and other migraine disorders), episodic and chronic tension-type headache, tension-type like headache, cluster headache, and chronic paroxysmal hemicrania are also CNS disorders. Visceral pain such as pancreatitis, intestinal cystitis, dysmenorrhea, irritable Bowel syndrome, Crohn's disease, biliary colic, ureteral colic, myocardial infarction and pain syndromes of the pelvic cavity, e.g., vulvodynia, orchialgia, urethral syndrome and prostatodynia are also CNS disorders.

Compounds that are modulators of CRTH2 are useful for the treatment of neuropathic pain, for example as described in WO05102338. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; back pain, non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; pain related to chronic alcoholism, hypothyroidism, uremia, or vitamin deficiencies; pain related to compression of the nerves (ie. Carpal Tunnel Syndrome), and pain resulting from physical trauma, amputation/phantom limb pain), cancer, toxins or chronic inflammatory conditions. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful

sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

TXA2 related therapeutic methods

Compounds which are modulators of thromboxane A₂ (TXA₂) receptor can be used for the prevention or treatment of indications related to an altered TXA₂ receptor function including, but not limited to the following: cerebral circulatory disorders, cerebral infarction, cerebral haemorrhages, cerebral vascular thrombosis, thromboembolisms, cerebral stroke, shock, ischemic heart diseases, myocardial infarction, acute heart failure, vasospastic disorders, angina pectoris, hypertension, atherosclerosis, arteriosclerosis, arteriosclerosis obliterans, thromboangiitis obliterans, hyperlipidemia, cholesterol ester storage disease and atheroma in vein grafts, reperfusion salvage disorders, for example after ischaemic injury, diabetic nephropathy, diabetic neuropathy and hypertriglyceridemia caused by diabetes, proliferative processes in occlusive vascular diseases (including prevention of arterial restenosis after angioplasty, post-surgical thickening of vascular walls), ischemic peripheral blood vessel diseases, postoperative thrombosis and to accelerate the dilation of transplanted blood vessels after an operation; platelet functional disorders; asthma, bronchial asthma, bronchospasms, pulmonary hypertension; prevention and treatment of hepatic and intestinal damage; renal disease (e.g., hydronephrosis, transplant rejection, and renal nephritis); an immune system activation of coagulation, pain, asthma, angiogenesis associated with a developing tumor, a method of preventing or delaying the onset of an inflammatory disorder mediated by TXA₂, allergic diseases; preeclampsia and preterm labor; degenerative processes in penile tissue, e.g. insufficiency of erectile tissue caused by e.g. alcoholism or nicotine abuse; nerve cell denaturation caused by amyloid β protein and nerve cell death caused by axonotmesis, central nervous system diseases, nerve degeneration diseases, nerve cell denaturation, amyloid β protein-induced nerve cell denaturation, nerve cell death,

axotomesis-induced nerve cell death and, in particular, dementia of Alzheimer type (as mentioned in the following documents US6407096, US20040152695A1, WO0030683A1, WO9502408A1, WO9205782A1, EP0744950B1, EP0484581B1, EP0240107B1, EP0668279B1, EP0522887A1).

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CysLT2 related therapeutic methods

Compounds which are modulators of CysLT2 can be used for the prevention or treatment of indications related to an altered cysteinyl leukotriene receptor function including, but not limited to the following: immune disorders, inflammatory disorders; and allergic disorders such as seasonal rhinitis, perennial vasomotor rhinitis, acute urticaria, chronic urticaria, atopic dermatitis, contact dermatitis, pruritus, angioedema, conjunctivitis, chronic bronchitis, systemic anaphylaxis, serum sickness, bronchial asthma, food allergies, and related inflammatory diseases including inflammatory bowel disease, and psoriasis, rheumatoid disorders (rheumatoid arthritis), hypersensitivity disorders, immunodeficiency or pseudoallergies (ie. intolerance to aspirin or other non-steroidal antiinflammatory drugs), allergy, angiogenesis, respiratory distress syndrome, Crohn's disease, ulcers, ulcerative colitis, benign prostatic hypertrophy, edema, disorders related to growth, development, cell growth, differentiation, tissue repair and the release of hormones, neurotransmitters, and cytokines, blood and bone homeostasis (osteoporosis); and gastrointestinal disorders (especially for gastro cytoprotection). The compounds are useful for the diagnosis and treatment of psychotic and neurologic disorders, such as central nervous system or peripheral nervous system disorders, including, for example delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome, epilepsy, schizophrenia, mood disorders (depression and bipolar disorder), anxiety, disorders of thought and volition, disorders of sleep and wakefulness, diseases of the motor unit like neurogenic and myopathic disorders, neurodegenerative disorders like Alzheimer's and Parkinson's disease, trauma, ischemia, sclerosis, various forms of encephalopathies, and demyelinating diseases; pain disorders or conditions, including, for example, vascular pain, including angina, ischemic muscle pain, migraine and cluster headaches (and other headache disorders), lumbar pain, pelvic pain, and sympathetic nerve activity including inflammation associated with

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arthritis; and exocrine and endocrine mediated disorders, including for example, disorders of airway electrolyte metabolism, i.e. cystic fibrosis, chronic airway infections, and other lung disorders. The compounds may also be use to treat or prevent atherosclerosis, peripheral arterial occlusive disease (PAOD), myocardial infarction (treatment, prevention, and prevention of reoccurrence), acute coronary syndrome, unstable angina, non-ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), obesity, diabetes and metabolic disease, urogenital disease, reproduction and sexual medicine, cancer, neoplastic and myeloproliferative diseases, vasculitic granulomatous diseases, sensory organ disorders, and hair loss. Uses of modulators of CysLT2 for these disorders are described in the following: WO0142269A1, WO0142269A1, WO0159118A1, WO0177149A2, WO04004773A1, WO04035741A2, WO05021518A1, WO8806886A1, WO9204325A1, WO9533839A1, WO9910529A1, US6878525, US5227378, US20010039037A1, US20020150901A1, US20040019080A1, US20050113408A1, EP0342664B1, EP0410241B1, EP0559871B1, EP0874047A3.

These compounds may also relate to disorders associated with tissues in which the receptors that they modulate are expressed, including, for example, brain, cortex, dorsal root ganglion (DRG) neurons, sciatic nerve, spinal cord, heart, kidney, gastro muscle, liver, lung, and, skin. Disorders involving the brain include, but are not limited to, disorders involving neurons, and disorders involving glia, such as astrocytes, oligodendrocytes, ependymal cells, and microglia; cerebral edema, raised intracranial pressure and herniation, and hydrocephalus; malformations and developmental diseases, such as neural tube defects, forebrain anomalies, posterior fossa anomalies, and syringomyelia and hydromyelia; perinatal brain injury; cerebrovascular diseases, such as those related to hypoxia, ischemia, and infarction, including hypotension, hypoperfusion, and low-flow states--global cerebral ischemia and focal cerebral ischemia--infarction from obstruction of local blood supply, intracranial hemorrhage, including intracerebral (intraparenchymal) hemorrhage, subarachnoid hemorrhage and ruptured berry aneurysms, and vascular malformations, hypertensive cerebrovascular disease, including lacunar infarcts, slit hemorrhages, and hypertensive encephalopathy; infections, such as acute meningitis, including acute pyogenic (bacterial) meningitis and acute aseptic (viral)

meningitis, acute focal suppurative infections, including brain abscess, subdural empyema, and extradural abscess, chronic bacterial meningoen­cephalitis, including tuberculosis and mycobacterioses, neurosyphilis, and neuroborreliosis (Lyme disease), viral meningoen­cephalitis, including arthropod-borne (Arbo) viral encephalitis, Herpes simplex virus Type 1, Herpes simplex virus Type 2, Varicella-zoster virus (Herpes zoster), cytomegalovirus, poliomyelitis, rabies, and human immunodeficiency virus 1, including HIV- 1 meningoen­cephalitis (subacute encephalitis), vacuolar myelopathy, AIDS- associated myopathy, peripheral neuropathy, and AIDS in children, progressive multifocal leukoen­cephalopathy, subacute sclerosing panencephalitis, fungal

5 meningoen­cephalitis, other infectious diseases of the nervous system; transmissible spongiform encephalopathies (prion diseases); demyelinating diseases, including multiple sclerosis, multiple sclerosis variants, acute disseminated encephalomyelitis and acute necrotizing hemorrhagic encephalomyelitis, and other diseases with demyelination; degenerative diseases, such as degenerative diseases affecting the cerebral cortex,

10 including Alzheimer disease and Pick disease, degenerative diseases of basal ganglia and brain stem, including Parkinsonism, idiopathic Parkinson disease (paralysis agitans), progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, including striatonigral degeneration, Shy-Drager syndrome, and olivopontocerebellar atrophy, and Huntington disease; spinocerebellar degenerations, including

20 spinocerebellar ataxias, including Friedreich ataxia, and ataxia telangiectasia, degenerative diseases affecting motor neurons, including amyotrophic lateral sclerosis (motor neuron disease), bulbospinal atrophy (Kennedy syndrome), and spinal muscular atrophy; inborn errors of metabolism, such as leukodystrophies, including Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy, Pelizaeus- Merzbacher

25 disease, and Canavan disease, mitochondrial encephalomyopathies, including Leigh disease and other mitochondrial encephalomyopathies; toxic and acquired metabolic diseases, including vitamin deficiencies such as thiamine (vitamin B 1) deficiency and vitamin B 12 deficiency, neurologic sequelae of metabolic disturbances, including hypoglycemia, hyperglycemia, and hepatic encephatopathy, toxic disorders, including

30 carbon monoxide, methanol, ethanol, and radiation, including combined methotrexate and radiation-induced injury; tumors, such as gliomas, including astrocytoma, including

fibrillary (diffuse) astrocytoma and glioblastoma multiforme, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and brain stem glioma, oligodendroglioma, and ependymoma and related paraventricular mass lesions, neuronal tumors, poorly differentiated neoplasms, including medulloblastoma, other parenchymal tumors, including primary brain lymphoma, germ cell tumors, and pineal parenchymal tumors, meningiomas, metastatic tumors, paraneoplastic syndromes, peripheral nerve sheath tumors, including schwannoma, neurofibroma, and malignant peripheral nerve sheath tumor (malignant schwannoma), and neurocutaneous syndromes (phakomatoses), including neurofibromatosis, including Type I neurofibromatosis (NF 0 and TYPE 2 neurofibromatosis (NF2), tuberous sclerosis, and Von Hippel Lindau disease.

Disorders of the peripheral nervous system include, inflammatory neuropathies, such as, immune-mediated neuropathies (i.e. Guillain-Barre syndrome); infectious polyneuropathies, such as, leprosy, diphtheria, varicella-zoster virus; hereditary neuropathies, such as, hereditary motor and sensory neuropathy I, HMSN II, Dejerine-Sottas Disease; acquired metabolic and toxic neuropathies, such as, peripheral neuropathy in adult-onset diabetes mellitus, metabolic and nutritional peripheral neuropathies, neuropathies associated with malignancy, toxic neuropathies; traumatic neuropathies; and tumors of the peripheral nerve.

Disorders involving the kidney include, but are not limited to, congenital anomalies including, but not limited to, cystic diseases of the kidney, that include but are not limited to, cystic renal dysplasia., autosomal dominant (adult) polycystic kidney disease, autosomal recessive (childhood) polycystic kidney disease, and cystic diseases of renal medulla, which include, but are not limited to, medullary sponge kidney, and nephronophthisis-uremic medullary cystic disease complex, acquired (dialysis associated) cystic disease, such as simple cysts; glomerular diseases including pathologies of glomerular injury that include, but are not limited to, in situ immune complex deposition, that includes, but is not limited to, anti-GBM nephritis, Heymann nephritis, and antibodies against planted antigens, circulating immune complex nephritis, antibodies to glomerular cells, cell-mediated immunity in glomerulonephritis, activation of alternative complement pathway, epithelial cell injury, and pathologies involving mediators of glomerular injury including cellular and soluble mediators, acute glomerulonephritis,

such as acute proliferative (poststreptococcal, postinfectious) glomerulonephritis, including but not limited to, poststreptococcal glomerulonephritis and nonstreptococcal acute glomerulonephritis, rapidly progressive (crescentic) glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis (membranous nephropathy), minimal change disease (lipoid nephrosis), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, IgA nephropathy (Berger disease), focal proliferative and necrotizing glomerulonephritis (focal glomerulonephritis), hereditary nephritis, including but not limited to, Alport syndrome and thin membrane disease (benign familial hematuria), chronic glomerulonephritis, glomerular lesions associated with systemic disease, including but not limited to, systemic lupus erythematosus, Henoch-Schonlein purpura, bacterial endocarditis, diabetic glomerulosclerosis, amyloidosis, fibrillary and immunotactoid glomerulonephritis, and other systemic disorders; diseases affecting tubules and interstitium, including acute tubular necrosis and tubulointerstitial nephritis, including but not limited to, pyelonephritis and urinary tract infection, acute pyelonephritis, chronic pyelonephritis and reflux nephropathy, urinary retention, and tubulointerstitial nephritis induced by drugs and toxins, including but not limited to, acute drug-induced interstitial nephritis, analgesic abuse nephropathy, nephropathy associated with nonsteroidal anti inflammatory drugs, and other tubulointerstitial diseases including, but not limited to, urate nephropathy, hypercalcemia and nephrocalcinosis, and multiple myeloma; diseases of blood vessels including benign nephrosclerosis, malignant hypertension and accelerated nephrosclerosis, renal artery stenosis, and thrombotic microangiopathies including, but not limited to, classic (childhood) hemolytic-uremic syndrome, adult hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura, idiopathic HUS/TTP, and other vascular disorders including, but not limited to, atherosclerotic ischemic renal disease, atheroembolic renal disease, sickle cell disease nephropathy, diffuse cortical necrosis, and renal infarcts; urinary tract obstruction (obstructive uropathy); urolithiasis (renal calculi, stones); and tumors of the kidney including, but not limited to, benign tumors, such as renal papillary adenoma, renal fibroma or hamartoma (renomedullary interstitial cell tumor), angiomyolipoma, and oncocytoma, and malignant tumors, including renal cell carcinoma (hypernephroma, adenocarcinoma of kidney), which includes urothelial carcinomas of renal pelvis.

Disorders involving the heart, include but are not limited to, heart failure, including but not limited to, cardiac hypertrophy, left- sided heart failure, and right sided heart failure; ischemic heart disease, including but not limited to atherosclerosis, peripheral arterial occlusive disease (PAOD), angina pectoris, myocardial infarction, chronic ischemic heart disease, and sudden cardiac death; hypertensive heart disease, including but not limited to, systemic (left- sided) hypertensive heart disease and pulmonary (right-sided) hypertensive heart disease; valvular heart disease, including but not limited to, valvular degeneration caused by calcification, such as calcific aortic stenosis, calcification of a congenitally bicuspid aortic valve, and mitral annular calcification, and myxomatous degeneration of the mitral valve (mitral valve prolapse), rheumatic fever and rheumatic heart disease, infective endocarditis, and noninfected vegetations, such as nonbacterial thrombotic endocarditis and endocarditis of systemic lupus erythematosus (Libman- Sacks disease), carcinoid heart disease, and complications of artificial valves; myocardial disease, including but not limited to dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and myocarditis; pericardial disease, including but not limited to, pericardial effusion and hemopericardium and pericarditis, including acute pericarditis and healed pericarditis, and rheumatoid heart disease; neoplastic heart disease, including but not limited to, primary cardiac tumors, such as myxoma, lipoma, papillary fibroelastoma, rhabdomyoma, and sarcoma, and cardiac effects of noncardiac neoplasms; congenital heart disease, including but not limited to, left-to-right shunts--late cyanosis, such as atrial septal defect, ventricular septal defect, patent ductus arteriosus, and atrioventricular septal defect, right-to-left shunts--early cyanosis, such as tetralogy of fallot, transposition of great arteries, truncus arteriosus, tricuspid atresia, and total anomalous pulmonary venous connection, obstructive congenital anomalies, such as coarctation of aorta, pulmonary stenosis and atresia, and aortic stenosis and atresia, and disorders involving cardiac transplantation.

Diseases of the skin, include but are not limited to, disorders of pigmentation, photoageing, and melanocytes, including but not limited to, vitiligo, freckle, melasma, lentigo, nevocellular nevus, dysplastic nevi, and malignant melanoma; benign epithelial tumors, including but not limited to, seborrheic keratoses, acanthosis nigricans,

fibroepithelial polyp, epithelial cyst, keratoacanthoma, and adnexal (appendage) tumors; premalignant and malignant epidermal tumors, including but not limited to, actinic keratosis, squamous cell carcinoma, basal cell carcinoma, and merkel cell diseases, including but not limited to, pemphigus, bullous pemphigoid, dermatitis herpetiformis, and noninflammatory blistering diseases: epidermolysis bullosa and porphyria; disorders of epidermal appendages, including but not limited to, acne vulgaris; panniculitis, including but not limited to, erythema nodosum and erythema induratum; and infection and infestation, such as verrucae, molluscum contagiosum, impetigo, superficial fungal infections, psoriasis, and arthropod bites, stings, and infestations.

Disorders involving the liver include, but are not limited to, hepatic injury; jaundice and cholestasis, such as bilirubin and bile formation; hepatic failure and cirrhosis, such as cirrhosis, portal hypertension, including ascites, portosystemic shunts, and splenomegaly; infectious disorders, such as viral hepatitis, including hepatitis A-E infection and infection by other hepatitis viruses, clinicopathologic syndromes, such as the carrier state, asymptomatic infection, acute viral hepatitis, chronic viral hepatitis, and fulminant hepatitis; autoimmune hepatitis; drug- and toxin-induced liver disease, such as alcoholic liver disease; inborn errors of metabolism and pediatric liver disease, such as hemochromatosis, Wilson disease, α_1 antitrypsin deficiency, and neonatal hepatitis; intrahepatic biliary tract disease, such as secondary biliary cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis, and anomalies of the biliary tree; circulatory disorders, such as impaired blood flow into the liver, including hepatic artery compromise and portal vein obstruction and thrombosis, impaired blood flow through the liver, including passive congestion and centrilobular necrosis and peliosis hepatis, hepatic vein outflow obstruction, including hepatic vein thrombosis (Budd-Chiari syndrome) and veno-occlusive disease; hepatic disease associated with pregnancy, such as preeclampsia and eclampsia, acute fatty liver of pregnancy, and intrahepatic cholestasis of pregnancy; hepatic complications of organ or bone marrow transplantation, such as drug toxicity after bone marrow transplantation, graft-versus-host disease and liver rejection, and nonimmunologic damage to liver allografts; tumors and tumorous conditions, such as nodular hyperplasias, adenomas, and malignant tumors, including primary carcinoma of the liver and metastatic tumors.

Disorders involving the lung and respiratory system include, but are not limited to, congenital anomalies; atelectasis; diseases of vascular origin, such as pulmonary congestion and edema, including hemodynamic pulmonary edema and edema caused by microvascular injury, adult respiratory distress syndrome (diffuse alveolar damage), pulmonary embolism, hemorrhage, and infarction, and pulmonary hypertension and vascular sclerosis; chronic obstructive pulmonary disease, such as emphysema, chronic bronchitis, asthma, chronic asthma, aspirin-induced asthma, bronchial asthma, and bronchiectasis; allergic rhinitis; pneumonia (e.g., interstitial myositis, etc.), severe acute respiratory syndrome (SARS), acute respiratory distress syndrome (ARDS), allergic rhinitis, sinusitis (e.g., acute sinusitis, chronic sinusitis, etc.), diffuse interstitial (infiltrative, restrictive) diseases, such as pneumoconioses, sarcoidosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary eosinophilia (pulmonary infiltration with eosinophilia), Bronchiolitis obliterans-organizing pneumonia, diffuse pulmonary hemorrhage syndromes, including Goodpasture syndrome, idiopathic pulmonary hemosiderosis and other hemorrhagic syndromes, pulmonary involvement in collagen vascular disorders, and pulmonary alveolar proteinosis; complications of therapies, such as drug-induced lung disease, radiation-induced lung disease, and lung transplantation; tumors, such as bronchogenic carcinoma, including paraneoplastic syndromes, bronchioloalveolar carcinoma, neuroendocrine tumors, such as bronchial carcinoid, miscellaneous tumors, and metastatic tumors; pathologies of the pleura, including inflammatory pleural effusions, noninflammatory pleural effusions, pneumothorax, and pleural tumors, including solitary fibrous tumors (pleural fibroma) and malignant mesothelioma. The compounds may also be used as expectorant agents or cough suppressants.

25 DAO Related Therapeutic Methods

Compounds described herein, e.g., that inhibit DAO can be used to treat memory or cognitive disorders or to enhance memory or cognitive function, e.g., in patients that are not suffering from a disorder associated with memory loss or impairment of cognitive function.

The patient can be suffering from one or more disorders chosen from short term memory, loss of long term memory, Alzheimer's Disease, and mild cognitive impairment. The patient can be suffering from or at risk of developing impairment of cognitive function associated with treatment with a therapeutic agent or one or more disorders chosen from:

5 vascular dementia, Huntington's Disease, hydrocephalus, depression, bipolar disorder, amnesia, AIDS-related dementia, Pick's Disease, Creutzfeldt-Jakob Syndrome, and Parkinson's Disease. The compounds can be administered with a second agent, e.g., tacrine, donepezil hydrochloride, galantamine, rivastigmine, a cholinesterase inhibitor, an NMDA receptor antagonist, a M1 muscarinic receptor antagonist, vitamin E/tocopherol, a

10 statin, CX516, aripipazole, CPI-1189, leteprenim potassium, phenserine tartrate, pravastatin, conjugated estrogen, risperidone, SB737552, SR 57667, or SR 57746

The compounds can be used to treat benign forgetfulness, a mild tendency to be unable to retrieve or recall information that was once registered, learned, and stored in memory.

15 Benign forgetfulness typically affects individuals over 40 and can be recognized by standard assessment instruments such as the Wechsler Memory Scale (Russell, 1975, *J. Consult Clin. Psychol.* 43:800-809).

The compounds can be used for treating AD. Methods for diagnosing AD are known in

20 the art. For example, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease-and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria can be used to diagnose AD (McKhann et al. 1984 *Neurology* 34:939-944). The patient's cognitive function can be assessed by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog;

25 Rosen et al., 1984, *Am. J. Psychiatry* 141:1356-1364).

The compounds can be used to treat neuropsychiatric disorders such as schizophrenia, autism, attention deficit disorder (ADD), and attention deficit-hyperactivity disorder (ADHD). They may be useful for treating mood disorders; anxiety related disorders;

30 eating disorders; substance-abuse related disorders; personality disorders; and other mental disorders.

The compounds can be used to treat cognitive and memory impairment associated with head injury or trauma, sometimes referred to as amnesic disorder due to a general medical condition.

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The compounds can also be used to treat conditions and disorders that include, but are not limited to, childhood learning disorders, and neurodegenerative diseases and disorders, such as MLS (cerebellar ataxia), ataxia, amyotrophic lateral sclerosis, Down syndrome, multi-infarct dementia, status epilepticus, contusive injuries (e.g. spinal cord injury and head injury), viral infection induced neurodegeneration, (e.g. AIDS, encephalopathies), epilepsy, benign forgetfulness, and closed head injury. The compounds may also be useful for the treatment of neurotoxic injury that follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospasm, hypoglycemia, amnesia, hypoxia, anoxia, perinatal asphyxia and cardiac arrest.

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The compounds can be used for the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that

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precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; back pain, non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; pain related to chronic alcoholism, hypothyroidism, uremia, or vitamin deficiencies; pain related to compression of the nerves (ie. Carpal Tunnel Syndrome), and pain resulting

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from physical trauma, amputation/phantom limb pain), cancer, toxins or chronic inflammatory conditions. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased

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sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal,

cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

- 5 The compounds are administered in combination with a second compound useful for slowing or reducing cognitive impairment or memory loss or increasing cognitive function or memory.

The compound can be a component of a pharmaceutical composition comprising an agent
10 for the treatment of memory loss (e.g., tacrine (Cognex®), donepezil hydrochloride (Aricept®), galantamine (Reminyl®), rivastigmine (Exelon®), a cholinesterase inhibitor, an NMDA receptor antagonist (e.g., memantine), a M1 muscarinic receptor antagonist, vitamin E/tocopherol, a statin (e.g., lovastatin), CX516 (Ampalex®; Cortex Pharmaceuticals, Irvine, CA), aripipazole (Bristol-Meyers Squibb, Lawrenceville, NJ),
15 CPI-1189 (Centaur Pharmaceuticals, Sunnyvale, CA), leteprenim potassium (Neotrofin®; NeoTherapeutics, Inrine, CA), phenserine tartrate (Axonyx, New York, NY), pravastatin (Pravachol®, Bristol-Meyers Squibb, Lawrenceville, NJ), conjugated estrogen (Premain®, Wyeth, Philadelphia, PA), risperidone (Risperdal®, Johnson & Johnson Pharmaceuticals Research and Development, Raritan, NJ), SB271046 (GlaxoSmithKline, Philadelphia, PA), SB737552 (GlaxoSmithKline, Philadelphia, PA), SR 57667 (Sanofi-Synthelabo, New York, NY), and SR 57746 (Sanofi-Synthelabo, New York, NY)).
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The compounds described herein can be administered with D-serine or an analog thereof (e.g., a salt of D-serine, an ester of D-serine, alkylated D-serine, or a precursor of D-serine). They can administered with an anti-psychotic, an anti-depressant or a
25 psychostimulant.

Treatments for depression can be used in combination with the compounds described herein. Suitable anti-depressants include: tricyclic antidepressants (TCAs); monoamine
30 oxidase inhibitors (MAOIs); serotonin selective reuptake inhibitors (SSRIs); dual serotonin and norepinephrine reuptake inhibitors; serotonin-2 antagonism/reuptake

inhibitors; α_2 /serotonin-2/serotonin-3 antagonists; and selective norepinephrine and dopamine reuptake inhibitors.

Anti-psychotic drugs can be used in combination with the compounds described herein.

5 Such treatments include: neuroleptics (e.g., chlorpromazine (Thorazine®); atypical neuroleptics (clozapine (Clozaril®)); risperidone (Risperdal®); and olanzapine (Zyprexa®).

10 Certain of the useful compounds inhibit the activity of D-aspartate oxidase (DDO), an enzyme that oxidizes D-Asp, D-Glu, D-Asn, D-Gln, D-Asp-dimethyl-ester and N-methyl-D-Asp.

The compounds can be administered in combination with a DAO or DDO inhibitor or antagonists such as those described in U.S. Application 20030166554, hereby
15 incorporated by reference. Suitable DDO inhibitors can include: aminoethylcysteine-ketimine (AECK, thialysine ketimine, 2H-1,4-thiazine-5,6-dihydro-3-carboxylic acid, S-aminoethyl-L-cysteine ketimine, 2H-1,4-Thiazine-3-carboxylic acid, 5,6-dihydro-); aminoethylcysteine (thialysine); cysteamine; pantetheine; cystathionine; and S-adenosylmethionine.

20

Administration of Compounds

The compounds can be used alone or in combination with other compounds used to treat inflammatory disorders. Combination therapies are useful in a variety of situations, including where an effective dose of one or more of the agents used in the combination
25 therapy is associated with undesirable toxicity or side effects when not used in combination. This is because a combination therapy can be used to reduce the required dosage or duration of administration of the individual agents.

Thus, the compounds can be used in a co-therapy with a second agent, e.g., an anti-inflammatory agent. Anti-inflammatory agents which can be used in co-therapy include:
30 NSAIDs, compounds which are leukotriene biosynthesis inhibitors, 5-lipoxygenase (LO)

inhibitors or 5-lipoxygenase activating protein (FLAP) antagonist (e.g., masoprocol, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, and flezelastine hydrochloride, enazadrem phosphate, bunaprolast, ABT-761, fenleuton, tepoxalin, Abbott-79175, Abbott-85761, a N- (5-substituted)-thiophene-2-alkylsulfonamide, 2,6-di-tert-butylphenolhydrazones, a methoxytetrahydropyrans such as Zeneca ZD-2138, the compound SB-210661, a pyridinyl- substituted 2-cyanonaphthalene compound such as L-739,010, a 2-cyanoquinoline compound such as L-746,530, or an indole or quinoline compound such as MK-591, MK-886, and BAY s x 1005), p38 inhibitors (e.g., SB203580 and Vertex compound VX745), LTB₄ antagonists and LTA₄ hydrolase inhibitors, CRTH2 modulators (e.g., ramatroban), steroids or corticosteroids (e.g., beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, bunedoside, butixocort, dexamethasone, flunisolide, fluocortin, fluticasone, fluticasone propionate, hydrocortisone, methylprednisolone, mometasone, predonisolone, predonisone, tipredane, tixocortal, triamcinolone, and triamcinolone acetonide), and other compounds including: Bayer compound BAY1005 (CA registry 128253-31-6), Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY-223982, LY-233469, and LY-255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SmithKline SKF-104493. Such anti-inflammatory drugs may also include steroids, in particular, glucocorticosteroids, such as budesonide, beclomethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate; or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 173, 90, 99 and 101), WO 03/035668, WO 03/048181, WO 03/062259, WO 03/064445 and 1 WO 03/072592; non-steroidal glucocorticoid receptor agonists, such as those described in WO 00/00531, WO 02/10143, WO 03/082280, WO 03/082787, WO 03/104195 and WO 04/005229; LTB₄ antagonists, such as those described in U.S. Patent No. 5,451,700; LTD₄ antagonists, such as montelukast and zafirlukast; PDE4 inhibitors, such as cilomilast (Aristo GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer),

SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), KW 4490 (Kyowa Hakko Kogyo), WO 03/104204, WO 03/104205, WO 04/000814, WO 04/000839 and WO 04005258 (Merck), as well as those described in
5 WO 98/18796 and I WO 03/39544; A2a agonists, such as those described in EP 1052264, EP 1241176, EP 409595A2, WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO
10 01/94368, WO 02/00676, WO 02/22630, WO 02/96462 and WO 03/086408; A2b antagonists, such as those described in WO 02/42298; and beta (O-2 adrenoceptor agonists, such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol, fenoterol, procaterol, formoterol, bitolterol mesylate, pirbuterol, and chiral enantiomer and pharmaceutically acceptable salts thereof; and compounds (in free or salt or solvate
15 form) of formula (I) of WO 00/75114.

The compounds can be used in combination with selective COX-2 inhibitors, e.g., meloxicam, Celecoxib, Valdecoxib, Parecoxib, Rofecoxib, Etoricoxib, and Lumaricoxib.

The compounds can be used in a co-therapy with an agent used to treat an anxiety disorders, including: benzodiazepines (e.g., Xanax®, Librium®), SSRIs (e.g., Prozac®,
20 Zoloft®), monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs, e.g., amitriptyline).

The compounds can be used in combination with anti-infectives such as fusidic acid and anti-fungals such as clotrimazole (both for the treatment of atopic dermatitis).

The compounds can be used in a co-therapy with an agent used to treat rheumatoid
25 arthritis including etanercept (Enbrel®) and infliximab (Remicade®).

The compounds can also be used in a co-therapy with a second agent that has analgesic activity. Analgesics which can be used in co-therapy include, but are not limited to: NSAIDs (e.g., acetaminophen, acetaminophen, acetyl salicylic acid, alclofenac,

alminoprofen, apazone, aspirin, azapropazone, benoxaprofen, bezpiperylon, bucloxic acid, carprofen, clidanac, diclofenac, diclofenac, diflunisal, diflusinal, etodolac, fenbufen, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, flufenisal, fluprofen, flurbiprofen, flurbiprofen, furofenac, ibufenac, ibuprofen,

5 indomethacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketoprofen, ketorolac, meclofenamic acid, meclofenamic acid, mefenamic acid, mefenamic acid, miroprofen, mofebutazone, nabumetone oxaprozin, naproxen, naproxen, niflumic acid, oxaprozin, oxpinac, oxyphenbutazone, phenacetin, phenylbutazone, phenylbutazone, piroxicam, pirprofen, pranoprofen, sudoxicam, tenoxicam, sulfasalazine, sulindac,

10 sulindac, suprofen, tiaprofenic acid, tiopinac, tioxaprofen, tolifenamic acid, tolmetin, tolmetin, zidometacin, zomepirac, and zomepirac), a non-narcotic analgesic such as tramadol, an opioid or narcotic analgesic (e.g., APF112, beta funaltrexamine, buprenorphine, butorphanol, codeine, cypridine, dezocine, dihydrocodeine, diphenyloxyate, enkephalin pentapeptide, fedotozine, fentanyl, hydrocodone,

15 hydromorphone, lignocaine, levorphanol, loperamide, meperidine, mepivacaine, methadone, methyl naloxone, morphine, nalbuphine, nalmefene, naloxonazine, naloxone, naltrexone, naltrindole, nor-binaltorphimine, oxycodone, oxymorphone, pentazocine, propoxyphene, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033, SSR-241585), CCK receptor antagonists (e.g., loxiglumide), NK3 receptor

20 antagonists (e.g., NKP-608C, talnetant (SB-233412), D-418, osanetant SR-142801, SSR-241585), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid receptor agonists and antagonists, cannabinoid receptor agonists (e.g., arvanil), sialorphan, compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH₂; WO 01/019849 A1), Tyr-Arg (kyotorphin), CCK receptor

25 agonists (e.g., caerulein), conotoxin peptides, peptide analogs of thymulin, dexloxiglumide (the R-isomer of loxiglumide; WO 88/05774), and analgesic peptides (e.g., endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance P).

Other agents which can be used in combination with compounds described herein for

30 treating, for example, neuropathic pain include, but are not limited to: (i) an opioid analgesic, e. g. morphine, heroin, hydromorphone, oxymorphone, levorphanol,

levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine; (ii) a nonsteroidal antiinflammatory drug (NSAID), e. g. aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin or zomepirac, or a pharmaceutically acceptable salt thereof; (iii) a barbiturate sedative, e. g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal or thiopental or a pharmaceutically acceptable salt thereof; (iv) a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam or a pharmaceutically acceptable salt thereof; (v) an H1 antagonist having a sedative action, e. g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine or a pharmaceutically acceptable salt thereof; (vi) a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone or a pharmaceutically acceptable salt thereof; (vii) a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadrine or a pharmaceutically acceptable salt thereof; (viii) an NMDA receptor antagonist, e. g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone or cis-4- (phosphonomethyl)-2-piperidinecarboxylic or a pharmaceutically acceptable salt thereof; (ix) an alpha-adrenergic, e. g. doxazosin, tamsulosin, clonidine or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline; (x) a tricyclic antidepressant, e. g. desipramine, imipramine, amitriptyline or nortriptyline; (xi) an anticonvulsant, e. g. carbamazepine, sodium valproate, or valproate; (xii) a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (aR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapitant or 3-[[2-methoxy-5-

(trifluoromethoxy) phenyl]methylamino]-2-phenyl-piperidine (2S,3S); (xiii) a muscarinic antagonist, e. g. oxybutin, tolterodine, propiverine, trospium chloride or darifenacin; (xiv) a COX-2 inhibitor, e. g. celecoxib, rofecoxib or valdecoxib; (xv) a non-selective COX inhibitor (preferably with GI protection), e. g. nitroflurbiprofen (HCT-1026); (xvi) a coal-
5 tar analgesic, in particular paracetamol; (xvii) a neuroleptic such as droperidol; (xviii) a vanilloid receptor agonist (e. g. resiniferatoxin) or antagonist (e. g. capsazepine); (xix) a beta-adrenergic such as propranolol; (xx) a local anaesthetic, such as mexiletine; (xxi) a corticosteroid, such as dexamethasone (xxii) a serotonin receptor agonist or antagonist; (xxiii) a cholinergic (nicotinic) analgesic; (xxiv) Tramadol (trade mark); (xxv) a PDEV
10 inhibitor, such as sildenafil, vardenafil or tadalafil; (xxvi) an alpha-2-delta ligand such as gabapentin or pregabalin; and (xxvii) a cannabinoid.

In addition, certain antidepressants can be used in co-therapy either because they have analgesic activity or are otherwise beneficial to use in combination with an analgesic.

15 Examples of such anti-depressants include: selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, sertraline), serotonin-norepinephrine dual uptake inhibitors, venlafaxine and nefazadone. Certain anti-convulsants have analgesic activity and are useful in co-therapy. Such anti-convulsants include: gabapentin, carbamazepine, phenytoin, valproate, clonazepam, topiramate and lamotrigine. Such agents are
20 considered particularly useful for treatment of neuropathic pain, e.g., treatment of trigeminal neuralgia, postherpetic neuralgia, and painful diabetic neuropathy. Additional compounds useful in co-therapy include: alpha-2-adrenergic receptor agonists (e.g., tizanidine and clonidine), mexiletine, corticosteroids, compounds that block the NMDA (N-methyl-D-aspartate) receptor (e.g. dextromethorphan, ketamine, and amantadine),
25 glycine antagonists, carisoprodol, cyclobenzaprine, various opiates, nonopioid antitussive (e.g. dextromethorphan, carmiphen, caramiphen and carbetapentane), opioid antitussives (e.g. codeine, hydrocodone, metaxolone. The compounds can also be combined with inhalable gaseous nitric oxide (for treating pulmonary vasoconstriction or airway
30 constriction), a thromboxane A2 receptor antagonist, a stimulant (i.e. caffeine), an H₂ – antagonist (e.g. ranitidine), an antacid (e.g. aluminum or magnesium hydroxide), an antiflatulent (e.g. simethicone), a decongestant (e.g. phenylephrine,

phenylpropanolamine, pseudophedrine, oxymetazoline, oxymetazoline hydrochloride, ephinephrine, naphazoline, naphazoline hydrochloride, xylometazoline, xylometazoline hydrochloride, tetrahydrozoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride, propylhexedrine, or levodesoxyephedrine), a

5 prostaglandin (e.g. misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol), a diuretic, a sedating or non-sedating histamine H1 receptor antagonists/antihistamines (i.e. any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: - 4

10 astemizole, acetaminophen, acrivastine, antazoline, astemizole, azatadine, azelastine, astemizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chlorpheniramine maleate, cimetidine, clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, desloratidine, loratidine dextrorphanamine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine succinate, doxylamine, ebastine, efletirizine, epinastine, farnotidine, fexofenadine,

15 hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norastemizole, noraztemizole, phenindamine, pheniramine, picumast, promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimoprazine, tripelenamine, and triprolidine; an antagonist of histamine type 4 receptors; a 5HT1

20 agonist, such as a triptan (e.g. sumatriptan or naratriptan), an adenosine A1 agonist, an EP ligand, a sodium channel blocker (e.g. lamotrigine), a substance P antagonist (e.g. an NK antagonist), a cannabinoid, a 5-lipoxygenase inhibitor, a leukotriene receptor antagonist/leukotriene antagonists/LTD4 or LTC4 or LTB4 or LTE4 antagonists (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the

25 interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafirlukast, verlukast (MK-679), montelukast, montelukast sodium (Singulair®), pranlukast, iralukast (CGP 45715A), pobilukast, BAY x 7195, SKB-106,203, phenothiazin-3-Is such as L-651,392, amidino compounds such as CGS-25019c, benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260,

30 ablukast, RG-12525, Ro-245913, and compounds described as having LTD4 antagonizing activity described in US 5,565,473, a DMARD (e.g. methotrexate), a

neurone stabilising antiepileptic drug, a mono-aminergic uptake inhibitor (e.g. venlafaxine), a matrix metalloproteinase inhibitor (the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10),
5 and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline), a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor, an inhibitor of the release, or action, of tumor necrosis factor, an antibody therapy, such as a monoclonal antibody therapy, an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator (e.g. interferon), a local
10 anaesthetic, a known FAAH inhibitor (e.g., PMSF, URB532, URB597, or BMS-1, as well as those described in those described in WO04033652, US6462054, US20030092734, US20020188009, US20030195226, and WO04033422), an antidepressant (e.g., VPI-013), a fatty acid amide (e.g. anandamide, N-palmitoyl ethanolamine, N-oleoyl ethanolamide, 2-arachidonoylglycerol, or oleamide), arvanil,
15 analogs of anandamide and arvanil as described in US 20040122089, and a proton pump inhibitor (e.g., omeprazole, esomeprazole, lansoprazole, pantorazole and rabeprazole).

The compound can also be used in a co-therapy with a second agent that is a cannabinoid receptor antagonist to prevent and/or treat obesity and other appetite related disorders.

20

Agents may also be coadministered with one or more of the following:

an immunostimulatory nucleic acids which contain an immunostimulatory motif or backbone that induces Th1 immune response and/or suppresses a Th2 immune response
25 such as CpG motifs, poly-G motifs and T-rich motifs. Examples of immunostimulatory nucleic acids are disclosed in US20030087848;

inactivating antibodies (e.g., monoclonal or polyclonal) to interleukins (e.g., IL-4 and IL-5 (for example see Leckie et al. 2000 *Lancet* 356:2144));

30

soluble chemokine receptors (e.g. recombinant soluble IL-4 receptor (Steinke and Borish 2001 *Respiratory Research* 2:66));

chemokine receptor modulators including but not limited to antagonists of chemokine

- 5 receptor superfamilies (e.g. CCR1 (e.g., CP-481,715 (Gladue et al. *J Biol Chem* 278:40473)), CCR2, CCR2A, CCR2B, CCR3 (e.g., UCB35625 (Sabroe et al. *J Biol Chem* 2000 275:25985), CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX3CR1 for the C-X3-C family, as well as the XC family.) These
- 10 modulators include those compounds described in US20060052413, US20060025432, WO0039125A1, WO02070523A1, WO03035627A1, WO03084954A1, WO04011443A1, WO04014875A1, WO04018425A1, WO04018435A1, WO04026835A1, WO04026880A1, WO04039376A1, WO04039377A1, WO04039787A1, WO04056773A1, WO04056808A1, WO05021513A1,
- 15 WO04056809A1, EP1541573A1, WO05040167A1, WO05058881A1, WO05073192A1, WO05070903A2, WO05101989A2, WO06024823, WO06001751, WO06001752 and EP1571146A1; PGD₂ receptor antagonists including, but not limited to, compounds described as having PGD₂ antagonizing activity in United States Published Applications US20020022218, US20010051624, and US20030055077, PCT Published Applications
- 20 W09700853, W09825919, WO03066046, WO03066047, WO03101961, WO03101981, WO04007451, WO0178697, WO04032848, WO03097042, WO03097598, WO03022814, WO03022813, and WO04058164, European Patent Applications EP945450 and EP944614, and those listed in: Torisu et al. 2004 *Bioorg Med Chem Lett* 14:4557, Torisu et al. 2004 *Bioorg Med Chem Lett* 2004 14:4891, and Torisu et al. 2004
- 25 *Bioorg & Med Chem* 2004 12:4685;

adhesion molecule inhibitors including VLA-4 antagonists;

purinergic receptor antagonists such as P2X7 receptor antagonists disclosed in

- 30 WO06025783;

immunosuppressants such as cyclosporine (cyclosporine A, Sandimmune® Neoral®), tacrolimus (FK-506, Prograf®), pimecrolimus, rapamycin (sirolimus, Rapamune®) and other FK-506 type immunosuppressants, and mycophenolate, e.g., mycophenolate mofetil (CellCept®);

5

β-agonists including but not limited to: albuterol (Proventil®, Salbutamol®, Ventolin®), bambuterol, bitoterol, clenbuterol, fenoterol, formoterol, isoetharine (Bronkosol®, Bronkometer®), metaproterenol (Alupent®, Metaprel®), pitbuterol (Maxair®), reproterol, rimiterol, salmeterol, terbutaline (Brethaire®, Brethine®, Bricanyl®), adrenalin, isoproterenol (Isuprel®), epinephrine bitartrate (Primatene®), ephedrine, orciprenlaine, fenoterol and isoetharine;

10

β2-agonist-corticosteroid combinations including but not limited to: salmeterol-fluticasone (Advair®), formoterol-budesonid (Symbicort®);

15

a bronchodilator including but not limited to methylxanthanines such as theophylline and aminophylline;

a mast cell stabilizer including but not limited to cromolyn, cromolyn sodium, sodium cromoglycate, nedocromil, and proxicromil

20

an anticholinergic including but not limited to: atropine, benztropine, biperiden, flutropium, hyoscyamine, hyoscine, ilutropium, ipratropium, ipratropium bromide, methscopolamine, oxybutinin, rispenzepine, scopolamine, oxitropium bromide, tiotropium bromide, glycopyrrrolate, pirenzepine, telenzepine, tiotropium salts and CHF 4226 (Chiesi), and also those described in WO 01/04118, WO 02/51841, WO 02/53564, WO 03/00840, 1 19. WO 03/87094, WO 04/05285, WO 02/00652, WO 03/53966, EP 424021, U.S. Patent No. 5,171,744, U.S. Patent No. 3,714,357 and WO 03/33495;

25

an anti-tussive including but not limited to: dextromethorphan, codeine, and hydromorphone;

30

a decongestant including but not limited to: pseudoephedrine and phenylpropanolamine;

an expectorant including but not limited to: guaifenesin, guaicol sulfate, terpin, ammonium chloride, glycerol guaicolate, and iodinated glycerol;

5

a PDE inhibitor including but not limited to fluticasone, denbutyllene, pivalamilast, roflumilast, zardaverine, cilomilast, and rolipram;

a recombinant humanized monoclonal antibody including but not limited to Omalizumab (xolair®) and talizumab (tnx-901);

10

a lung surfactant including but not limited to dsc-104;

a cardiovascular agent such as a calcium channel blocker, a beta- adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxifylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor;

15

antithrombotic agents, such as thrombolytic agents (e.g., streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, β -blockers (e.g., atenolol), β -adrenergic agonists (e.g., isoproterenol), ACE inhibitors and vasodilators (e.g., sodium nitroprusside, nicardipine hydrochloride, nitroglycerin and enalaprilat);

20

anti-diabetic agents such as insulin and insulin mimetics, sulfonylureas (e.g., glyburide, meglitinide), biguanides, e.g., metformin (Glucophage®), α -glucosidase inhibitors (acarbose), PPAR- γ agonists and/or thiazolidinone compounds, e.g., rosiglitazone (Avandia®), troglitazone (Rezulin®), ciglitazone, pioglitazone (Actos®) and englitazone;

25

30

anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate;

5 preparations of interferon (such as interferon β -I α , interferon β -I β , and alpha, beta, and gamma interferons);

gold compounds such as auranohm, aurantium, auranofin and aurothioglucose;

10 cytokinemodulators including but not limited to inhibitors of tumor necrosis factor (TNF) (e.g. etanercept (Enbrel®), antibody therapies such as adalimumab, CDP-870, orthoclone (OKT3), daclizumab (Zenapax®), basiliximab (Simulec®), infliximab (Remicade®), D2E6 TNF antibody), interleukins (including IL1, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL11, IL12, IL13, IL14, IL15, IL16, IL17 and compounds as described in WO05042502A1 and WO05061465A1), interleukin antagonists or inhibitors such as
15 anakinra (kineret) and pentoxifylline.

lubricants or emollients such as petrolatum and lanolin, keratolytic agents, vitamin D₃ derivatives (e.g., thalidomide or a derivative thereof, dithranol, calcipotriene and calcipotriol (Dovonex®)), PUVA, anthralin (Drithrocreme®), etretinate (Tegison®) and
20 isotretinoin;

nicotinic acid or another nicotinic acid receptor agonist (for example, one can coadminister a CRTH2 or DP-1 antagonist to reduce, prevent or eliminate flushing associated with administration with nicotinic acid or a nicotinic receptor agonist). In
25 certain embodiments a compound described herein which is selective for antagonizing DP-1 activity is coadministered with nicotinic acid or a nicotinic acid receptor agonist to prevent and/or treat atherosclerosis in the absence of substantial flushing. In other embodiments a compound described herein which is selective for antagonizing CRTH2 activity is coadministered with nicotinic acid or a nicotinic acid receptor agonist to
30 prevent and/or treat atherosclerosis in the absence of substantial flushing;

antibacterial agents such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, ozalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz;

a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a COMT inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, propentofylline or metrifonate;

an agent for the treatment of cancer, for example, (i) an antiproliferative/antineoplastic drug, such as an alkylating agent (e.g., cisplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (e.g., an antifolate like fluoropyrimidine, 5-fluorouracil, tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (e.g., an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (e.g., a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (e.g., an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (e.g., tamoxifen, toremifene, raloxifene, droloxifene or idoxifene), an estrogen receptor down regulator (e.g., fulvestrant), an antiandrogen (e.g., bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (e.g., goserelin, leuporelin or buserelin), a progestogen (e.g., megestrol acetate), an aromatase inhibitor (e.g., anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5-alpha-reductase such

as finasteride; (iii) an agent which inhibits cancer cell invasion (e.g., a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function (e.g. monoclonal antibodies like Herceptin (trastuzumab) or Erbitux (cetuximab), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (e.g., an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (e.g., the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (e.g., linomide, an inhibitor of integrin $\alpha v \beta 3$ function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, e.g., one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, e.g., approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, e.g., ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell energy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies;

multiple sclerosis therapeutic agents such as interferon β - I β (Betaseron®), interferon β -I α (Avonex®), azathioprine (Imurek®, Imuran®), glatiramer acetate (Capoxone®), a glucocorticoid (e.g., prednisolone) and cyclophosphamide; and

- 5 other compounds such as 5-aminosalicylic acid and prodrugs thereof, DNA-alkylating agents (e.g., cyclophosphamide, ifosfamide), antimetabolites (e.g., azathioprine, 6-mercaptopurine, methotrexate, a folate antagonist, and 5-fluorouracil, a pyrimidine antagonist), microtubule disruptors (e.g., vincristine, vinblastine, paclitaxel, colchicine, nocodazole and vinorelbine), DNA intercalators (e.g., doxorubicin, daunomycin and cisplatin), DNA synthesis inhibitors such as hydroxyurea, DNA cross-linking agents, e.g., mitomycin C, hormone therapy (e.g., tamoxifen, and flutamide), leflunomide, hydroxychloroquine, d- penicillamine, diacerein, intra-articular therapies such as hyaluronic acid derivatives, nutritional supplements such as glucosamine, combinations of aminosalicylates and sulfapyndine such as mesalazine, balsalazide, and
- 15 olsalazine, immunomodulatory agents such as the thiopurines, a tryptase inhibitor, a platelet activating factor (PAP) antagonist, an interleukin converting enzyme (ICE) inhibitor, an inosine-5'-monophosphate dehydrogenase (IMPDH inhibitor), cathepsin, a kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine/threonine kinase inhibitor (such as an
- 20 inhibitor of a MAP kinase such as p38, INK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase), a glucose-6 phosphate dehydrogenase inhibitor, a xanthine oxidase inhibitor (e.g. allopurinol), an uricosuric agent (e.g. probenecid, sulenpyrazone or benzbromarone), a growth hormone secretagogue, a transforming growth factor, a platelet-derived growth factor, a fibroblast
- 25 growth factor (e.g. basic fibroblast growth factor, a granulocyte macrophage colony stimulating factor (GM-CSF), capsaicin cream, an elastase inhibitor (such as UT-77 or ZD-0892), a TNF-alpha converting enzyme inhibitor (TACE), an agent modulating the function of Toll-like receptors (TLR), an inhibitor of transcription factor activation such as NFkB, API, or STATS, and cytostatic agents (e.g., imatinib (STI571, Gleevec®) and
- 30 rituximab (Rituxan®)).

Compounds described herein (e.g. DAO inhibitors) may be administered in combination with one or more d-amino acids (for example, one or more of D-Asp, D-Ser, D-Ala, D-Leu and D-Pro) when administered to treat, for example, a CNS related disorder.

5 Combination Therapy

Combination therapy can be achieved by administering two or more agents, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in
10 conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or
15 within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

20 Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

25 Administration

The agents, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings,

absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

The agent can be in the form of a pharmaceutically acceptable salt. Such salts are prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Examples of salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. In some embodiments, the salt can be an ammonium, calcium, magnesium, potassium, or sodium salt. Examples of salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. In some embodiments, the salt can be an ammonium, calcium, magnesium, potassium, or sodium salt. Examples of salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, benethamine, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, diethanolamine, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, epolamine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, meglumine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and troamine, tromethamine. Examples of other salts include tris, arecoline, arginine, barium, betaine, bismuth, chlorprocaine, choline, clemizole, deanol, imidazole, and morpholineethanol. In one embodiment are tris salts.

The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, pellet, gel, paste, syrup, bolus, electuary, slurry, capsule; powder; granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a liposomal formulation (see, e.g., EP 736299) or in some other form. Orally

administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active
5 ingredient therein. The agents can also be administered by capsitol delivery technology, rectal suppository or parenterally.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine
10 the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or
15 controlled release of the active ingredient therein. The pharmaceutical compositions may include a "pharmaceutically acceptable inert carrier", and this expression is intended to include one or more inert excipients, which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like. If desired, tablet dosages of the disclosed compositions may be coated by standard
20 aqueous or nonaqueous techniques, "Pharmaceutically acceptable carrier" also encompasses controlled release means.

Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors,
25 desiccants, plasticizers, dyes, and the like. Any such optional ingredient must be compatible with the compound to insure the stability of the formulation.

The composition may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose,
30 stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and

hydrates thereof, and amino acids, for example alanine, glycine and betaine, and peptides and proteins, for example albumen.

5 Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as:

10 BINDERS: alginic acid, cellulose and its derivatives (*e.g.* ethyl cellulose, cellulose acetate, carboxymethyl cellulose, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), citric acid monohydrate, corn starch, gelatin, guar gum, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™ such as AVICEL-PH-101™, -103™, and 105™ sold by FMC Corporation, Marcus Hook, PA USA), natural and synthetic gums
15 such as acacia, other alginates, other starches, polyethylene oxide, polyvinyl alcohol, polyvinyl pyrrolidone, potato starch, powdered tragacanth, pre-gelatinized starch (*e.g.* STARCH 1500® and STARCH 1500 LM®, sold by Colorcon), sodium alginate, or mixtures thereof;

20 FILLERS: aluminum magnesium hydroxide, aluminum oxide, calcium carbonate (*e.g.* granules or powder), calcium dihydroxide, calcium sulfate (*e.g.* granules or powder), dextrates, dextrose, dibasic calcium phosphate, dibasic calcium phosphate anhydrous, fructose (granules or powder), honey, hydrous lactose, iron oxides (*e.g.* yellow, black, red, *e.g.* ferric oxide), kaolin, lactose, lactose and aspartame, lactose and cellulose,
25 lactose and microcrystalline cellulose, lactose anhydrate, lactose monohydrate, magnesium aluminate, magnesium carbonate, magnesium hydroxide, maltodextrin, maltose, mannitol, microcrystalline cellulose, microcrystalline cellulose & guar gum, molasses, powdered cellulose, pre-gelatinized starch, silicic acid, silicic anhydride, silicified microcrystalline cellulose, sodium chloride, sorbitol, soybean lecithin, starch,
30 sucrose, talc, triacetin, tribasic calcium phosphate, xanthar gum, or mixtures thereof;

DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, clays, croscarmellose sodium, crospovidone, gums (like gellan), lactose monohydrate, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, other algin, other celluloses, other starches, polacrilin potassium, potato or tapioca starch, povidone, pre-gelatinized starch, simethicone emulsion, sodium starch glycolate, or mixtures thereof

SURFACTANTS: Tween 80 or polyoxyethylene-polyoxypropylene copolymer, polyoxyethylene sorbitan, or mixtures thereof;

LUBRICANTS: a coagulated aerosol of synthetic silica (Degussa Co. Plano TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), agar, calcium stearate, ethyl laurate, ethyl oleate, glycerin, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), light mineral oil, magnesium stearate, mannitol, mineral oil, other glycols, palmitic acid, polyethylene glycol, sodium lauryl sulfate, sodium stearyl fumarate, sorbitol, stearic acid, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), talc, vegetable based fatty acids lubricant, zinc stearate, or mixtures thereof;

ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof;

ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, polysorbate, sorbic acid, thimersol, thymo, or mixtures thereof;

COATING AGENTS: candellilla wax, caruba wax, cellulose acetate phthalate, ethylcellulose, gelatin, gellan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methylcellulose (hypromellose), maltodextrin, methacrylates, methylcellulose, microcrystalline cellulose and carrageenan, microcrystalline wax, pharmaceutical glaze, polyethylene glycol (e.g. polyethylene glycol

8000, polyethylene glycol 3000), polyvinyl acetate phthalate, shellac, sodium carboxymethyl cellulose, sucrose, titanium dioxide, or mixtures thereof; COLORANTS: FD&C blue no. 1, D&C yellow #10 aluminum lake, FD&C yellow #6/sunset yellow FCF aluminum lake, FD&C carmine aluminum lake and FD&C blue #1, or mixtures thereof; and

ANTIOXIDANTS: butylated hydroxyanisole, sodium ascorbate, sodium metabisulfate, malic acid, citric acid, ascorbic acid, butylated hydroxytoluene, vitamin C, propyl gallate, or mixtures thereof.

The formulation can also include other excipients and categories thereof including but not limited to L-histidine, Pluronic®, Poloxamers (such as Lutrol® and Poloxamer 188), ascorbic acid, glutathione, permeability enhancers (e.g. lipids, sodium cholate, acylcarnitine, salicylates, mixed bile salts, fatty acid micelles, chelators, fatty acid, surfactants, medium chain glycerides), protease inhibitors (e.g. soybean trypsin inhibitor, organic acids), pH lowering agents and absorption enhancers effective to promote bioavailability (including but not limited to those described in US6086918 and US5912014), creams and lotions (like maltodextrin and carrageenans); materials for chewable tablets (like dextrose, fructose, lactose monohydrate, lactose and aspartame, lactose and cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose and guar gum, sorbitol crystalline); parenterals (like mannitol and povidone); plasticizers (like dibutyl sebacate, plasticizers for coatings, polyvinylacetate phthalate); powder lubricants (like glyceryl behenate); soft gelatin capsules (like sorbitol special solution); spheres for coating (like sugar spheres); spherization agents (like glyceryl behenate and microcrystalline cellulose); suspending/gelling agents (like carrageenan, gellan gum, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, xanthan gum); sweeteners (like aspartame, aspartame and lactose, dextrose, fructose, honey, maltodextrin, maltose, mannitol, molasses, sorbitol crystalline, sorbitol special solution, sucrose); wet granulation agents (like calcium carbonate, lactose anhydrous, lactose monohydrate, maltodextrin, mannitol, microcrystalline cellulose, povidone, starch), caramel, carboxymethylcellulose sodium, cherry cream flavor and cherry flavor, citric

acid anhydrous, citric acid, confectioner's sugar, D&C Red No. 33, D&C Yellow #10 Aluminum Lake, disodium edetate, ethyl alcohol 15%, FD&C Yellow No. 6 aluminum lake, FD&C Blue #1 Aluminum Lake, FD&C Blue No. 1, FD&C blue no. 2 aluminum lake, FD&C Green No.3, FD&C Red No. 40, FD&C Yellow No. 6 Aluminum Lake, FD&C Yellow No. 6, FD&C Yellow No.10, glycerol palmitostearate, glyceryl monostearate, indigo carmine, lecithin, manitol, methyl and propyl parabens, mono ammonium glycyrrhizinate, natural and artificial orange flavor, pharmaceutical glaze, poloxamer 188, Polydextrose, polysorbate 20, polysorbate 80, polyvidone, pregelatinized corn starch, pregelatinized starch, red iron oxide, saccharin sodium, sodium carboxymethyl ether, sodium chloride, sodium citrate, sodium phosphate, strawberry flavor, synthetic black iron oxide, synthetic red iron oxide, titanium dioxide, and white wax.

Solid oral dosage forms may optionally be treated with coating systems (e.g. Opadry® film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS-1-7040), and black ink (S-1-8106).

The dose range for adult humans is generally from 0.005 mg to 10 g/day orally. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound described herein which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

A dosage unit (e.g. an oral dosage unit) can include from, for example, 1 to 30 µg, 1 to 40 µg, 1 to 50 µg, 1 to 100 µg, 1 to 200 µg, 1 to 300 µg, 1 to 400 µg, 1 to 500 µg, 1 to 600 µg, 1 to 700 µg, 1 to 800 µg, 1 to 900 µg, 1 to 1000 µg, 10 to 30 µg, 10 to 40 µg, 10 to 50 µg, 10 to 100 µg, 10 to 200 µg, 10 to 300 µg, 10 to 400 µg, 10 to 500 µg, 10 to 600 µg, 10 to 700 µg, 10 to 800 µg, 10 to 900 µg, 10 to 1000 µg, 100 to 200 µg, 100 to 300 µg, 100

to 400 µg, 100 to 500 µg, 100 to 600 µg, 100 to 700 µg, 100 to 800 µg, 100 to 900 µg, 100 to 1000 µg, 100 to 1250 µg, 100 to 1500 µg, 100 to 1750 µg, 100 to 2000 µg, 100 to 2250 µg, 100 to 2500 µg, 100 to 2750 µg, 100 to 3000 µg, 200 to 300 µg, 200 to 400 µg, 200 to 500 µg, 200 to 600 µg, 200 to 700 µg, 200 to 800 µg, 200 to 900 µg, 200 to 1000 µg, 200 to 1250 µg, 200 to 1500 µg, 200 to 1750 µg, 200 to 2000 µg, 200 to 2250 µg, 200 to 2500 µg, 200 to 2750 µg, 200 to 3000 µg, 300 to 400 µg, 300 to 500 µg, 300 to 600 µg, 300 to 700 µg, 300 to 800 µg, 300 to 900 µg, 300 to 1000 µg, 300 to 1250 µg, 300 to 1500 µg, 300 to 1750 µg, 300 to 2000 µg, 300 to 2250 µg, 300 to 2500 µg, 300 to 2750 µg, 300 to 3000 µg, 400 to 500 µg, 400 to 600 µg, 400 to 700 µg, 400 to 800 µg, 400 to 900 µg, 400 to 1000 µg, 400 to 1250 µg, 400 to 1500 µg, 400 to 1750 µg, 400 to 2000 µg, 400 to 2250 µg, 400 to 2500 µg, 400 to 2750 µg, 400 to 3000 µg, 500 to 600 µg, 500 to 700 µg, 500 to 800 µg, 500 to 900 µg, 500 to 1000 µg, 500 to 1250 µg, 500 to 1500 µg, 500 to 1750 µg, 500 to 2000 µg, 500 to 2250 µg, 500 to 2500 µg, 500 to 2750 µg, 500 to 3000 µg, 600 to 700 µg, 600 to 800 µg, 600 to 900 µg, 600 to 1000 µg, 600 to 1250 µg, 600 to 1500 µg, 600 to 1750 µg, 600 to 2000 µg, 600 to 2250 µg, 600 to 2500 µg, 600 to 2750 µg, 600 to 3000 µg, 700 to 800 µg, 700 to 900 µg, 700 to 1000 µg, 700 to 1250 µg, 700 to 1500 µg, 700 to 1750 µg, 700 to 2000 µg, 700 to 2250 µg, 700 to 2500 µg, 700 to 2750 µg, 700 to 3000 µg, 800 to 900 µg, 800 to 1000 µg, 800 to 1250 µg, 800 to 1500 µg, 800 to 1750 µg, 800 to 2000 µg, 800 to 2250 µg, 800 to 2500 µg, 800 to 2750 µg, 800 to 3000 µg, 900 to 1000 µg, 900 to 1250 µg, 900 to 1500 µg, 900 to 1750 µg, 900 to 2000 µg, 900 to 2250 µg, 900 to 2500 µg, 900 to 2750 µg, 900 to 3000 µg, 1000 to 1250 µg, 1000 to 1500 µg, 1000 to 1750 µg, 1000 to 2000 µg, 1000 to 2250 µg, 1000 to 2500 µg, 1000 to 2750 µg, 1000 to 3000 µg, 2 to 500 µg, 50 to 500 µg, 3 to 100 µg, 5 to 20 µg, 5 to 100 µg, 50 µg, 100 µg, 150 µg, 200 µg, 250 µg, 300 µg, 350 µg, 400 µg, 450 µg, 500 µg, 550 µg, 600 µg, 650 µg, 700 µg, 750 µg, 800 µg, 850 µg, 900 µg, 950 µg, 1000 µg, 1050 µg, 1100 µg, 1150 µg, 1200 µg, 1250 µg, 1300 µg, 1350 µg, 1400 µg, 1450 µg, 1500 µg, 1550 µg, 1600 µg, 1650 µg, 1700 µg, 1750 µg, 1800 µg, 1850 µg, 1900 µg, 1950 µg, 2000 µg, 2050 µg, 2100 µg, 2150 µg, 2200 µg, 2250 µg, 2300 µg, 2350 µg, 2400 µg, 2450 µg, 2500 µg, 2550 µg, 2600 µg, 2650 µg, 2700 µg, 2750 µg, 2800 µg, 2850 µg, 2900 µg, 2950 µg, 3000 µg, 3250 µg, 3500 µg, 3750 µg, 4000 µg, 4250 µg, 4500 µg, 4750 µg, 5000 µg, 1 to 30 mg, 1 to 40 mg, 1 to 100 mg, 1 to 300 mg, 1 to 500 mg, 2 to

500 mg, 3 to 100 mg, 5 to 20 mg, 5 to 100 mg (e.g. 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg) of a compound described herein. In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g. with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day.

Combining two or more active ingredients in single dosage form results in the possibility of chemical interactions between the active drug substances. For example, acidic and basic active ingredients can react with each other and acidic active ingredients can facilitate the degradation of acid labile substances. Thus, in certain dosage forms, acidic and basic substances can be physically separated as two distinct or isolated layers in a compressed tablet, or in the core and shell of a press-coated tablet. Additional agents that are compatible with acidic as well as basic substances, have the flexibility of being placed in either layer. In certain multiple layer compositions at least one active ingredient can be enteric-coated. In certain embodiments thereof at least one active ingredient can be presented in a controlled release form. In certain embodiments where a combination of three or more active substances are used, they can be presented as physically isolated segments of a compressed multilayer tablet, which can be optionally film coated.

The therapeutic combinations described herein can be formulated as a tablet or capsule comprising a plurality of beads, granules, or pellets. All active ingredients including the vitamins of the combination are formulated into granules or beads or pellets that are further coated with a protective coat, an enteric coat, or a film coat to avoid the possible chemical interactions. Granulation and coating of granules or beads is done using techniques well known to a person skilled in the art. At least one active ingredient can

present in a controlled release form. Finally these coated granules or beads are filled into hard gelatin capsules or compressed to form tablets.

5 The therapeutic combinations described herein can be formulated as a capsule comprising microtablets or minitabets of all active ingredients. Microtablets of the individual agents can be prepared using well known pharmaceutical procedures of tablet making like direct compression, dry granulation or wet granulation. Individual microtablets can be filled into hard gelatin capsules. A final dosage form may comprise one or more microtablets of each individual component. The microtablets may be film coated or enteric coated.

10 The therapeutic combinations described herein can be formulated as a capsule comprising one or more microtablets and powder, or one or more microtablets and granules or beads. In order to avoid interactions between drugs, some active ingredients of a said combination can be formulated as microtablets and the others filled into capsules as a powder, granules, or beads. The microtablets may be film coated or enteric coated. At least one active ingredient can be presented in controlled release form.

20 The therapeutic combinations described herein can be formulated wherein the active ingredients are distributed in the inner and outer phase of tablets. In an attempt to divide chemically incompatible components of proposed combination, few interacting components are converted in granules or beads using well known pharmaceutical procedures in prior art. The prepared granules or beads (inner phase) are then mixed with outer phase comprising the remaining active ingredients and at least one pharmaceutically acceptable excipient. The mixture thus comprising inner and outer phase is compressed into tablets or molded into tablets. The granules or beads can be controlled release or immediate release beads or granules, and can further be coated using an enteric polymer in an aqueous or non-aqueous system, using methods and materials that are known in the art.

30 The therapeutic combinations described herein can be formulated as single dosage unit comprising suitable buffering agent. All powdered ingredients of said combination are

mixed and a suitable quantity of one or more buffering agents is added to the blend to minimize possible interactions.

The agents described herein, alone or in combination, can be combined with any
5 pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents,
10 microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

The agents can be a free acid or base, or a pharmacologically acceptable salt thereof.
15 Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants,
20 buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means

25 Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known
30 in the art, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, 1995.

Formulation

5 The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycolic acid (PLGA), poly-(l)-lactic-glycolic-tartaric acid (P(l)LGT) (WO 01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ϵ -caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used to implants that release a compound or
10 another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., U.S. 6,620,422). Other sustained release formulations are described in EP 0 467 389 A2, WO 93/241150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 9726015, WO 97/04744, and US20020019446. In such sustained release formulations microparticles of
15 compound are combined with microparticles of polymer. U.S. 6,011,011 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (where PEG 300 and PEG 400 are most preferred) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled release of the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326 151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S.
20 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224.

Controlled release formulations

In general, one can provide for controlled release of the agents described herein through
30 the use of a wide variety of polymeric carriers and controlled release systems including

erodible and non-erodible matrices, osmotic control devices, various reservoir devices, enteric coatings and multiparticulate control devices.

Matrix devices are a common device for controlling the release of various agents. In
5 such devices, the agents described herein are generally present as a dispersion within the polymer matrix, and are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of these devices may be dependent upon the solubility of the agent in the polymer matrix or, in the case of porous
10 matrices, the solubility in the sink solution within the pore network, and the tortuosity of the network. In one instance, when utilizing an erodible polymeric matrix, the matrix imbibes water and forms an aqueous-swollen gel that entraps the agent. The matrix then gradually erodes, swells, disintegrates or dissolves in the GI tract, thereby controlling release of one or more of the agents described herein. In non-erodible devices, the agent
15 is released by diffusion through an inert matrix.

Agents described herein can be incorporated into an erodible or non-erodible polymeric matrix controlled release device. By an erodible matrix is meant aqueous-erodible or
water-swallowable or aqueous-soluble in the sense of being either erodible or swallowable or
20 dissolvable in pure water or requiring the presence of an acid or base to ionize the polymeric matrix sufficiently to cause erosion or dissolution. When contacted with the aqueous environment of use, the erodible polymeric matrix imbibes water and forms an aqueous-swollen gel or matrix that entraps the agent described herein. The aqueous-swollen matrix gradually erodes, swells, disintegrates or dissolves in the environment of
25 use, thereby controlling the release of a compound described herein to the environment of use.

The erodible polymeric matrix into which an agent described herein can be incorporated may generally be described as a set of excipients that are mixed with the agent following
its formation that, when contacted with the aqueous environment of use imbibes water
30 and forms a water-swollen gel or matrix that entraps the drug form. Drug release may occur by a variety of mechanisms, for example, the matrix may disintegrate or dissolve

from around particles or granules of the agent or the agent may dissolve in the imbibed aqueous solution and diffuse from the tablet, beads or granules of the device. One ingredient of this water-swollen matrix is the water-swellaable, erodible, or soluble polymer, which may generally be described as an osmopolymer, hydrogel or water-swellaable polymer. Such polymers may be linear, branched, or crosslinked. The polymers may be homopolymers or copolymers. In certain embodiments, they may be synthetic polymers derived from vinyl, acrylate, methacrylate, urethane, ester and oxide monomers. In other embodiments, they can be derivatives of naturally occurring polymers such as polysaccharides (e.g. chitin, chitosan, dextran and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum and scleroglucan), starches (e.g. dextrin and maltodextrin), hydrophilic colloids (e.g. pectin), phosphatides (e.g. lecithin), alginates (e.g. ammonium alginate, sodium, potassium or calcium alginate, propylene glycol alginate), gelatin, collagen, and celluloses. Celluloses are cellulose polymer that has been modified by reaction of at least a portion of the hydroxyl groups on the saccharide repeat units with a compound to form an ester-linked or an ether-linked substituent. For example, the cellulosic ethyl cellulose has an ether linked ethyl substituent attached to the saccharide repeat unit, while the cellulosic cellulose acetate has an ester linked acetate substituent. In certain embodiments, the celluloses for the erodible matrix comprises aqueous-soluble and aqueous-erodible celluloses can include, for example, ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC). In certain embodiments, the celluloses comprises various grades of low viscosity (MW less than or equal to 50,000 daltons, for example, the Dow Methocel™ series E5, E15LV, E50LV and K100LY) and high viscosity (MW greater than 50,000 daltons, for example, E4MCR, E10MCR, K4M, K15M and K100M and the Methocel™ K series) HPMC. Other commercially available types of HPMC include the Shin Etsu Metolose 90SH series.

The choice of matrix material can have a large effect on the maximum drug concentration attained by the device as well as the maintenance of a high drug concentration. The matrix material can be a concentration-enhancing polymer, for example, as described in WO05/011634.

5

Other materials useful as the erodible matrix material include, but are not limited to, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT, Rohm America, Inc., Piscataway, New Jersey) and other acrylic acid derivatives such as homopolymers and copolymers of butylmethacrylate, 10 methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl) methacrylate, and (trimethylaminoethyl) methacrylate chloride.

15

The erodible matrix polymer may contain a wide variety of the same types of additives and excipients known in the pharmaceutical arts, including osmopolymers, osmagens, solubility-enhancing or-retarding agents and excipients that promote stability or processing of the device.

20

Alternatively, the agents of the present invention may be administered by or incorporated into a non-erodible matrix device. In such devices, an agent described herein is distributed in an inert matrix. The agent is released by diffusion through the inert matrix. Examples of materials suitable for the inert matrix include insoluble plastics (e.g. methyl acrylate-methyl methacrylate copolymers, polyvinyl chloride, polyethylene), hydrophilic polymers (e.g. ethyl cellulose, cellulose acetate, crosslinked polyvinylpyrrolidone (also 25 known as crospovidone)), and fatty compounds (e.g. carnauba wax, microcrystalline wax, and triglycerides). Such devices are described further in Remington: The Science and Practice of Pharmacy, 20th edition (2000).

30

Matrix controlled release devices may be prepared by blending an agent described herein and other excipients together, and then forming the blend into a tablet, caplet, pill, or other device formed by compressive forces. Such compressed devices may be formed

using any of a wide variety of presses used in the fabrication of pharmaceutical devices. Examples include single-punch presses, rotary tablet presses, and multilayer rotary tablet presses, all well known in the art. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000. The compressed device may be of any shape, including
5 round, oval, oblong, cylindrical, or triangular. The upper and lower surfaces of the compressed device may be flat, round, concave, or convex.

In certain embodiments, when formed by compression, the device has a strength of at least 5 Kiloponds (Kp)/cm² (for example, at least 7 Kp/cm²). Strength is the fracture
10 force, also known as the tablet hardness required to fracture a tablet formed from the materials, divided by the maximum cross-sectional area of the tablet normal to that force. The fracture force may be measured using a Schleuniger Tablet Hardness Tester, Model 6D. The compression force required to achieve this strength will depend on the size of the tablet, but generally will be greater than about 5 kP/cm². Friability is a well-know
15 measure of a device's resistance to surface abrasion that measures weight loss in percentage after subjecting the device to a standardized agitation procedure. Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability. Devices having a strength of greater than 5 kP/cm² generally are very robust, having a friability of less than 0.5%. Other methods for forming matrix controlled-release devices
20 are well known in the pharmaceutical arts. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

As noted above, the agents described herein may also be incorporated into an osmotic control device. Such devices generally include a core containing one or more agents as
25 described herein and a water permeable, non-dissolving and non-eroding coating surrounding the core which controls the influx of water into the core from an aqueous environment of use so as to cause drug release by extrusion of some or all of the core to the environment of use. In certain embodiments, the coating is polymeric, aqueous-permeable, and has at least one delivery port. The core of the osmotic device optionally
30 includes an osmotic agent which acts to imbibe water from the surrounding environment via such a semi-permeable membrane. The osmotic agent contained in the core of this

device may be an aqueous-swellaable hydrophilic polymer or it may be an osmogen, also known as an osmagent. Pressure is generated within the device which forces the agent(s) out of the device via an orifice (of a size designed to minimize solute diffusion while preventing the build-up of a hydrostatic pressure head). Nonlimiting examples of
5 osmotic control devices are disclosed in U. S. Patent Application Serial No. 09/495,061.

Osmotic agents create a driving force for transport of water from the environment of use into the core of the device. Osmotic agents include but are not limited to water- swellaable hydrophilic polymers, and osmogens (or osmagens). Thus, the core may include water-
10 swellaable hydrophilic polymers, both ionic and nonionic, often referred to as osmopolymers and hydrogels. The amount of water-swellaable hydrophilic polymers present in the core may range from about 5 to about 80 wt% (including for example, 10 to 50 wt%). Nonlimiting examples of core materials include hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO),
15 polyethylene glycol (PEG), polypropylene glycol (PPG), poly (2-hydroxyethyl methacrylate), poly (acrylic) acid, poly (methacrylic) acid, polyvinylpyrrolidone (PVP) and crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers and PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate, vinyl acetate, and the like, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose,
20 carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolat. Other materials include hydrogels comprising interpenetrating networks of polymers that may be formed by addition or by condensation polymerization,
25 the components of which may comprise hydrophilic and hydrophobic monomers such as those just mentioned. Water-swellaable hydrophilic polymers include but are not limited to PEO, PEG, PVP, sodium croscarmellose, HPMC, sodium starch glycolate, polyacrylic acid and crosslinked versions or mixtures thereof.

30 The core may also include an osmogen (or osmagent). The amount of osmogen present in the core may range from about 2 to about 70 wt% (including, for example, from 10 to 50

wt%). Typical classes of suitable osmogens are water-soluble organic acids, salts and sugars that are capable of imbibing water to thereby effect an osmotic pressure gradient across the barrier of the surrounding coating. Typical useful osmogens include but are not limited to magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, mannitol, xylitol, urea, sorbitol, inositol, raffinose, sucrose, glucose, fructose, lactose, citric acid, succinic acid, tartaric acid, and mixtures thereof. In certain embodiments, the osmogen is glucose, lactose, sucrose, mannitol, xylitol, sodium chloride, including combinations thereof.

The core may include a wide variety of additives and excipients that enhance the performance of the dosage form or that promote stability, tableting or processing. Such additives and excipients include tableting aids, surfactants, water-soluble polymers, pH modifiers, fillers, binders, pigments, disintegrants, antioxidants, lubricants and flavorants.

Nonlimiting examples of additives and excipients include but are not limited to those described elsewhere herein as well as microcrystalline cellulose, metallic salts of acids (e.g. aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, zinc stearate), pH control agents (e.g. buffers, organic acids, organic acid salts, organic and inorganic bases), fatty acids, hydrocarbons and fatty alcohols (e.g. stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmitol), fatty acid esters (e.g. glyceryl (mono- and di-) stearates, triglycerides, glyceryl (palmiticstearic) ester, sorbitan esters (e.g. sorbitan monostearate, saccharose monostearate, saccharose monopalmitate, sodium stearyl fumarate), polyoxyethylene sorbitan esters), surfactants (e.g. alkyl sulfates (e.g. sodium lauryl sulfate, magnesium lauryl sulfate), polymers (e.g. polyethylene glycols, polyoxyethylene glycols, polyoxyethylene, polyoxypropylene ethers, including copolymers thereof), polytetrafluoroethylene), and inorganic materials (e.g. talc, calcium phosphate), cyclodextrins, sugars (e.g. lactose, xylitol), sodium starch glycolate).

Nonlimiting examples of disintegrants are sodium starch glycolate (e.g., Explotab[™] CLV, (microcrystalline cellulose (e.g., Avicel[™]), microcrystalline silicified cellulose (e.g., ProSolv[™]), croscarmellose sodium (e.g., Ac-Di-Sol[™]). When the agent described herein is a solid amorphous dispersion formed by a solvent process, such additives may

be added directly to the spray-drying solution when forming an agent described herein/concentration-enhancing polymer dispersion such that the additive is dissolved or suspended in the solution as a slurry. Alternatively, such additives may be added following the spray-drying process to aid in forming the final controlled release device.

5

A nonlimiting example of an osmotic device consists of one or more drug layers containing an agent described herein, such as a solid amorphous drug/polymer dispersion, and a sweller layer that comprises a water-swellaable polymer, with a coating surrounding the drug layer and sweller layer. Each layer may contain other excipients such as
10 tableting aids, osmagents, surfactants, water-soluble polymers and water-swellaable polymers.

Such osmotic delivery devices may be fabricated in various geometries including bilayer (wherein the core comprises a drug layer and a sweller layer adjacent to each other),
15 trilayer (wherein the core comprises a sweller layer sandwiched between two drug layers) and concentric (wherein the core comprises a central sweller agent surrounded by the drug layer). The coating of such a tablet comprises a membrane permeable to water but substantially impermeable to drug and excipients contained within. The coating contains one or more exit passageways or ports in communication with the drug-containing
20 layer(s) for delivering the drug agent. The drug-containing layer(s) of the core contains the drug agent (including optional osmagents and hydrophilic water-soluble polymers), while the sweller layer consists of an expandable hydrogel, with or without additional osmotic agents.

25 When placed in an aqueous medium, the tablet imbibes water through the membrane, causing the agent to form a dispensable aqueous agent, and causing the hydrogel layer to expand and push against the drug-containing agent, forcing the agent out of the exit passageway. The agent can swell, aiding in forcing the drug out of the passageway. Drug can be delivered from this type of delivery system either dissolved or dispersed in the
30 agent that is expelled from the exit passageway.

The rate of drug delivery is controlled by such factors as the permeability and thickness of the coating, the osmotic pressure of the drug-containing layer, the degree of hydrophilicity of the hydrogel layer, and the surface area of the device. Those skilled in the art will appreciate that increasing the thickness of the coating will reduce the release rate, while any of the following will increase the release rate: increasing the permeability of the coating; increasing the hydrophilicity of the hydrogel layer; increasing the osmotic pressure of the drug-containing layer; or increasing the device's surface area.

Other materials useful in forming the drug-containing agent, in addition to the agent described herein itself, include HPMC, PEO and PVP and other pharmaceutically acceptable carriers. In addition, osmagents such as sugars or salts, including but not limited to sucrose, lactose, xylitol, mannitol, or sodium chloride, may be added. Materials which are useful for forming the hydrogel layer include sodium CMC, PEO (e.g. polymers having an average molecular weight from about 5,000,000 to about 7,500,000 daltons), poly (acrylic acid), sodium (polyacrylate), sodium croscarmellose, sodium starch glycolat, PVP, crosslinked PVP, and other high molecular weight hydrophilic materials.

In the case of a bilayer geometry, the delivery port(s) or exit passageway(s) may be located on the side of the tablet containing the drug agent or may be on both sides of the tablet or even on the edge of the tablet so as to connect both the drug layer and the sweller layer with the exterior of the device. The exit passageway(s) may be produced by mechanical means or by laser drilling, or by creating a difficult-to-coat region on the tablet by use of special tooling during tablet compression or by other means.

The osmotic device can also be made with a homogeneous core surrounded by a semipermeable membrane coating, as in US3845770. The agent described herein can be incorporated into a tablet core and a semipermeable membrane coating can be applied via conventional tablet-coating techniques such as using a pan coater. A drug delivery passageway can then be formed in this coating by drilling a hole in the coating, either by use of a laser or mechanical means. Alternatively, the passageway may be formed by

rupturing a portion of the coating or by creating a region on the tablet that is difficult to coat, as described above. In one embodiment, an osmotic device comprises: (a) a single-layer compressed core comprising: (i) an agent described herein, (ii) a hydroxyethylcellulose, and (iii) an osmagent, wherein the hydroxyethylcellulose is present in the core from about 2.0% to about 35% by weight and the osmagent is present from about 15% to about 70% by weight; (b) a water-permeable layer surrounding the core; and (c) at least one passageway within the water-permeable layer (b) for delivering the drug to a fluid environment surrounding the tablet. In certain embodiments, the device is shaped such that the surface area to volume ratio (of a water-swollen tablet) is greater than 0.6 mm^{-1} (including, for example, greater than 1.0 mm^{-1}). The passageway connecting the core with the fluid environment can be situated along the tablet band area. In certain embodiments, the shape is an oblong shape where the ratio of the tablet tooling axes, i.e., the major and minor axes which define the shape of the tablet, are between 1.3 and 3 (including, for example, between 1.5 and 2.5). In one embodiment, the combination of the agent described herein and the osmagent have an average ductility from about 100 to about 200 Mpa, an average tensile strength from about 0.8 to about 2.0 Mpa, and an average brittle fracture index less than about 0.2. The single-layer core may optionally include a disintegrant, a bioavailability enhancing additive, and/or a pharmaceutically acceptable excipient, carrier or diluent.

In certain embodiments, entrainment of particles of agents described herein in the extruding fluid during operation of such osmotic device is desirable. For the particles to be well entrained, the agent drug form is dispersed in the fluid before the particles have an opportunity to settle in the tablet core. One means of accomplishing this is by adding a disintegrant that serves to break up the compressed core into its particulate components. Nonlimiting examples of standard disintegrants include materials such as sodium starch glycolate (e. g., Explotab[™] CLV), microcrystalline cellulose (e. g., Avicel[™]), microcrystalline silicified cellulose (e. g., ProSol[™]) and croscarmellose sodium (e. g., Ac-Di-Sol[™]), and other disintegrants known to those skilled in the art. Depending upon the particular formulation, some disintegrants work better than others. Several disintegrants tend to form gels as they swell with water, thus hindering drug delivery

from the device. Non-gelling, non-swelling disintegrants provide a more rapid dispersion of the drug particles within the core as water enters the core. In certain embodiments, non-gelling, non-swelling disintegrants are resins, for example, ion-exchange resins. In one embodiment, the resin is Amberlite™ IRP 88 (available from Rohm and Haas, Philadelphia, PA). When used, the disintegrant is present in amounts ranging from about 1-25% of the core agent.

Water-soluble polymers are added to keep particles of the agent suspended inside the device before they can be delivered through the passageway(s) (e.g., an orifice). High viscosity polymers are useful in preventing settling. However, the polymer in combination with the agent is extruded through the passageway(s) under relatively low pressures. At a given extrusion pressure, the extrusion rate typically slows with increased viscosity. Certain polymers in combination with particles of the agent described herein form high viscosity solutions with water but are still capable of being extruded from the tablets with a relatively low force. In contrast, polymers having a low weight-average, molecular weight (< about 300,000) do not form sufficiently viscous solutions inside the tablet core to allow complete delivery due to particle settling. Settling of the particles is a problem when such devices are prepared with no polymer added, which leads to poor drug delivery unless the tablet is constantly agitated to keep the particles from settling inside the core. Settling is also problematic when the particles are large and/or of high density such that the rate of settling increases.

In certain embodiments, the water-soluble polymers for such osmotic devices do not interact with the drug. In certain embodiments the water-soluble polymer is a non-ionic polymer. A nonlimiting example of a non-ionic polymer forming solutions having a high viscosity yet still extrudable at low pressures is Natrosol™ 250H (high molecular weight hydroxyethylcellulose, available from Hercules Incorporated, Aqualon Division, Wilmington, DE; MW equal to about 1 million daltons and a degree of polymerization equal to about 3,700). Natrosol 250H™ provides effective drug delivery at concentrations as low as about 3% by weight of the core when combined with an osmagent. Natrosol 250H™ NF is a high-viscosity grade nonionic cellulose ether that is soluble in hot or cold

water. The viscosity of a 1% solution of Natrosol 250H using a Brookfield LVT (30 rpm) at 25°C is between about 1, 500 and about 2,500 cps.

In certain embodiments, hydroxyethylcellulose polymers for use in these monolayer osmotic tablets have a weight-average, molecular weight from about 300,000 to about 1.5 million. The hydroxyethylcellulose polymer is typically present in the core in an amount from about 2.0% to about 35% by weight.

Another example of an osmotic device is an osmotic capsule. The capsule shell or portion of the capsule shell can be semipermeable. The capsule can be filled either by a powder or liquid consisting of an agent described herein, excipients that imbibe water to provide osmotic potential, and/or a water-swellaable polymer, or optionally solubilizing excipients. The capsule core can also be made such that it has a bilayer or multilayer agent analogous to the bilayer, trilayer or concentric geometries described above.

Another class of osmotic device useful in this invention comprises coated swellable tablets, for example, as described in EP378404. Coated swellable tablets comprise a tablet core comprising an agent described herein and a swelling material, preferably a hydrophilic polymer, coated with a membrane, which contains holes, or pores through which, in the aqueous use environment, the hydrophilic polymer can extrude and carry out the agent. Alternatively, the membrane may contain polymeric or low molecular weight water-soluble porosigens. Porosigens dissolve in the aqueous use environment, providing pores through which the hydrophilic polymer and agent may extrude. Examples of porosigens are water-soluble polymers such as HPMC, PEG, and low molecular weight compounds such as glycerol, sucrose, glucose, and sodium chloride. In addition, pores may be formed in the coating by drilling holes in the coating using a laser or other mechanical means. In this class of osmotic devices, the membrane material may comprise any film-forming polymer, including polymers which are water permeable or impermeable, providing that the membrane deposited on the tablet core is porous or contains water-soluble porosigens or possesses a macroscopic hole for water ingress and

drug release. Embodiments of this class of sustained release devices may also be multilayered, as described, for example, in EP378404.

When an agent described herein is a liquid or oil, such as a lipid vehicle formulation, for example as described in WO05/011634, the osmotic controlled-release device may comprise a soft-gel or gelatin capsule formed with a composite wall and comprising the liquid formulation where the wall comprises a barrier layer formed over the external surface of the capsule, an expandable layer formed over the barrier layer, and a semipermeable layer formed over the expandable layer. A delivery port connects the liquid formulation with the aqueous use environment. Such devices are described, for example, in US6419952, US6342249, US5324280, US4672850, US4627850, US4203440, and US3995631.

The osmotic controlled release devices of the present invention can also comprise a coating. In certain embodiments, the osmotic controlled release device coating exhibits one or more of the following features: is water-permeable, has at least one port for the delivery of drug, and is non-dissolving and non-eroding during release of the drug formulation, such that drug is substantially entirely delivered through the delivery port(s) or pores as opposed to delivery primarily via permeation through the coating material itself. Delivery ports include any passageway, opening or pore whether made mechanically, by laser drilling, by pore formation either during the coating process or *in situ* during use or by rupture during use. In certain embodiments, the coating is present in an amount ranging from about 5 to 30 wt% (including, for example, 10 to 20 wt%) relative to the core weight.

One form of coating is a semipermeable polymeric membrane that has the port(s) formed therein either prior to or during use. Thickness of such a polymeric membrane may vary between about 20 and 800 μm (including, for example, between about 100 to 500 μm). The diameter of the delivery port (s) may generally range in size from 0.1 to 3000 μm or greater (including, for example, from about 50 to 3000 μm in diameter). Such port(s) may be formed post-coating by mechanical or laser drilling or may be formed *in situ* by

rupture of the coatings; such rupture may be controlled by intentionally incorporating a relatively small weak portion into the coating. Delivery ports may also be formed *in situ* by erosion of a plug of water-soluble material or by rupture of a thinner portion of the coating over an indentation in the core. In addition, delivery ports may be formed during
5 coating, as in the case of asymmetric membrane coatings of the type disclosed in US5612059 and US5698220. The delivery port may be formed *in situ* by rupture of the coating, for example, when a collection of beads that may be of essentially identical or of a variable agent are used. Drug is primarily released from such beads following rupture of the coating and, following rupture, such release may be gradual or relatively sudden.
10 When the collection of beads has a variable agent, the agent may be chosen such that the beads rupture at various times following administration, resulting in the overall release of drug being sustained for a desired duration.

Coatings may be dense, microporous or asymmetric, having a dense region supported by
15 a thick porous region such as those disclosed in US5612059 and US5698220. When the coating is dense the coating can be composed of a water-permeable material. When the coating is porous, it may be composed of either a water-permeable or a water-impermeable material. When the coating is composed of a porous water-impermeable material, water permeates through the pores of the coating as either a liquid or a vapor.
20 Nonlimiting examples of osmotic devices that utilize dense coatings include US3995631 and US3845770. Such dense coatings are permeable to the external fluid such as water and may be composed of any of the materials mentioned in these patents as well as other water-permeable polymers known in the art.

25 The membranes may also be porous as disclosed, for example, in US5654005 and US5458887 or even be formed from water-resistant polymers. US5120548 describes another suitable process for forming coatings from a mixture of a water-insoluble polymer and a leachable water-soluble additive. The porous membranes may also be formed by the addition of pore-formers as disclosed in US4612008. In addition, vapor-
30 permeable coatings may even be formed from extremely hydrophobic materials such as polyethylene or polyvinylidene difluoride that, when dense, are essentially water-

impermeable, as long as such coatings are porous. Materials useful in forming the coating include but are not limited to various grades of acrylic, vinyls, ethers, polyamides, polyesters and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration such as by crosslinking. Nonlimiting examples of suitable polymers (or crosslinked versions) useful in forming the coating include plasticized, unplasticized and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxiated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly (acrylic) acids and esters and poly- (methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. In various embodiments, the coating agent comprises a cellulosic polymer, in particular cellulose ethers, cellulose esters and cellulose ester-ethers, i.e., cellulosic derivatives having a mixture of ester and ether substituents, the coating materials are made or derived from poly (acrylic) acids and esters, poly (methacrylic) acids and esters, and copolymers thereof, the coating agent comprises cellulose acetate, the coating comprises a cellulosic polymer and PEG, the coating comprises cellulose acetate and PEG.

Coating is conducted in conventional fashion, typically by dissolving or suspending the coating material in a solvent and then coating by dipping, spray coating or by pan-coating. In certain embodiments, the coating solution contains 5 to 15 wt% polymer. Typical solvents useful with the cellulosic polymers mentioned above include but are not limited to acetone, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, ethylene glycol monoethyl ether, ethylene glycol

monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, 1,4-dioxane, tetrahydrofuran, diglyme, water, and mixtures thereof. Pore-formers and non-solvents (such as water, glycerol and ethanol) or plasticizers (such as diethyl phthalate) may also be added in any amount as long as the polymer remains soluble at the spray temperature. Pore-formers and their use in fabricating coatings are described, for example, in US5612059. Coatings may also be hydrophobic microporous layers wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed, for example, in US5798119. Such hydrophobic but water-vapor permeable coatings are typically composed of hydrophobic polymers such as polyalkenes, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. Hydrophobic microporous coating materials include but are not limited to polystyrene, polysulfones, polyethersulfones, polyethylene, polypropylene, polyvinyl chloride, polyvinylidene fluoride and polytetrafluoroethylene. Such hydrophobic coatings can be made by known phase inversion methods using any of vapor-quench, liquid quench, thermal processes, leaching soluble material from the coating or by sintering coating particles. In thermal processes, a solution of polymer in a latent solvent is brought to liquid-liquid phase separation in a cooling step. When evaporation of the solvent is not prevented, the resulting membrane will typically be porous. Such coating processes may be conducted by the processes disclosed, for example, in US4247498, US4490431 and US4744906. Osmotic controlled-release devices may be prepared using procedures known in the pharmaceutical arts. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

As further noted above, the agents described herein may be provided in the form of microparticulates, generally ranging in size from about 10 μ m to about 2mm (including, for example, from about 100 μ m to 1mm in diameter). Such multiparticulates may be packaged, for example, in a capsule such as a gelatin capsule or a capsule formed from an aqueous-soluble polymer such as HPMCAS, HPMC or starch; dosed as a suspension or slurry in a liquid; or they may be formed into a tablet, caplet, or pill by compression or

other processes known in the art. Such multiparticulates may be made by any known process, such as wet- and dry-granulation processes, extrusion/spheronization, roller-compaction, melt-congealing, or by spray-coating seed cores. For example, in wet-and dry- granulation processes, the agent described herein and optional excipients may be
5 granulated to form multiparticulates of the desired size. Other excipients, such as a binder (e. g., microcrystalline cellulose), may be blended with the agent to aid in processing and forming the multiparticulates. In the case of wet granulation, a binder such as microcrystalline cellulose may be included in the granulation fluid to aid in forming a suitable multiparticulate. See, for example, Remington : The Science and
10 Practice of Pharmacy, 20th Edition, 2000. In any case, the resulting particles may themselves constitute the therapeutic composition or they may be coated by various film-forming materials such as enteric polymers or water-swellaable or water-soluble polymers, or they may be combined with other excipients or vehicles to aid in dosing to patients.

15 In certain embodiments, it may be desirable to provide for the immediate release of one or more of the agents described herein, and the controlled release of one or more other agents. For example, in one embodiment, a compound described herein can be provided in an immediate release formulation together with a cotherapy agent described herein in a controlled release format. For example, in one embodiment, a compound described
20 herein can be provided in a controlled release format together with a cotherapy agent described herein in an immediate release format.

The agents can be incorporated into microemulsions, which generally are thermodynamically stable, isotropically clear dispersions of two immiscible liquids, such
25 as oil and water, stabilized by an interfacial film of surfactant molecules (Encyclopedia of Pharmaceutical Technology (New York: Marcel Dekker, 1992), volume 9). For the preparation of microemulsions, surfactant (emulsifier), co-surfactant (co-emulsifier), an oil phase and a water phase are necessary. Suitable surfactants include any surfactants that are useful in the preparation of emulsions, e.g., emulsifiers that are typically used in
30 the preparation of creams. The co-surfactant (or "co-emulsifier") is generally selected from the group of polyglycerol derivatives, glycerol derivatives and fatty alcohols.

Preferred emulsifier/co-emulsifier combinations are generally although not necessarily selected from the group consisting of: glyceryl monostearate and polyoxyethylene stearate; polyethylene glycol and ethylene glycol palmitostearate; and caprylic and capric triglycerides and oleoyl macrogolglycerides. The water phase includes not only water but
5 also, typically, buffers, glucose, propylene glycol, polyethylene glycols, preferably lower molecular weight polyethylene glycols (e.g., PEG 300 and PEG 400), and/or glycerol, and the like, while the oil phase will generally comprise, for example, fatty acid esters, modified vegetable oils, silicone oils, mixtures of mono- di- and triglycerides, mono- and di-esters of PEG (e.g., oleoyl macrogol glycerides), etc.

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The compounds described herein can be incorporated into pharmaceutically-acceptable nanoparticle, nanosphere, and nanocapsule formulations (Delie and Blanco-Prieto 2005 Molecule 10:65-80). Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland et al., 1987; Quintanar-Guerrero et al., 1998;
15 Douglas et al., 1987). To avoid side effects due to intracellular polymeric overloading, ultrafine particles (sized around 0.1 μm) can be designed using polymers able to be degraded in vivo (e.g. biodegradable polyalkyl-cyanoacrylate nanoparticles). Such particles are described in the prior art (Couvreur et al, 1980; 1988; zur Muhlen et al., 1998; Zambaux et al. 1998; Pinto-Alphandry et al., 1995 and U.S. Pat. No. 5,145,684).

20

The compounds described herein can be formulated with pH sensitive materials which may include those described in WO04041195 (including the seal and enteric coating described therein) and pH-sensitive coatings that achieve delivery in the colon including those described in US4910021 and WO9001329. US4910021 describes using a pH-
25 sensitive material to coat a capsule. WO9001329 describes using pH-sensitive coatings on beads containing acid, where the acid in the bead core prolongs dissolution of the pH-sensitive coating. U. S. Patent No. 5,175, 003 discloses a dual mechanism polymer mixture composed of pH-sensitive enteric materials and film-forming plasticizers capable of conferring permeability to the enteric material, for use in drug-delivery systems; a
30 matrix pellet composed of a dual mechanism polymer mixture permeated with a drug and sometimes covering a pharmaceutically neutral nucleus; a membrane-coated pellet

comprising a matrix pellet coated with a dual mechanism polymer mixture envelope of the same or different composition; and a pharmaceutical dosage form containing matrix pellets. The matrix pellet releases acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally about 5.0 or higher. The compounds described

5 herein may be formulated in the pH triggered targeted control release systems described in WO04052339. The compounds described herein may be formulated according to the methodology described in any of WO03105812 (extruded hydratable polymers); WO0243767 (enzyme cleavable membrane translocators); WO03007913 and WO03086297 (mucoadhesive systems); WO02072075 (bilayer laminated formulation

10 comprising pH lowering agent and absorption enhancer); WO04064769 (amidated peptides); WO05063157 (solid lipid suspension with pseudotropic and/or thixotropic properties upon melting); WO03035029 and WO03035041 (erodible, gastric retentive dosage forms); US5007790 and US5972389 (sustained release dosage forms); WO04112711 (oral extended release compositions); WO05027878, WO02072033, and

15 WO02072034 (delayed release compositions with natural or synthetic gum); WO05030182 (controlled release formulations with an ascending rate of release); WO05048998 (microencapsulation system); US Patent 5,952, 314 (biopolymer); US5108758 (glassy amylose matrix delivery); US 5840860 (modified starch based delivery). JP10324642 (delivery system comprising chitosan and gastric resistant material

20 such as wheat gliadin or zein); US5866619 and US6368629 (saccharide containing polymer); US 6531152 (describes a drug delivery system containing a water soluble core (Ca pectinate or other water-insoluble polymers) and outer coat which bursts (eg hydrophobic polymer-Eudragit)); US 6234464; US 6403130 (coating with polymer containing casein and high methoxy pectin; WO0174175 (Maillard reaction product);

25 WO05063206 (solubility increasing formulation); WO04019872 (transferring fusion proteins). The compounds described herein may be formulated using gastrointestinal retention system technology (GIRES; Merriam Pharmaceuticals). GIRES comprises a controlled-release dosage form inside an inflatable pouch, which is placed in a drug capsule for oral administration. Upon dissolution of the capsule, a gas-generating system

30 inflates the pouch in the stomach where it is retained for 16-24 hours, all the time releasing compounds described herein.

The compounds described herein can be formulated in an osmotic device including the ones disclosed in US4503030, US5609590 and US5358502. US4503030 discloses an osmotic device for dispensing a drug to certain pH regions of the gastrointestinal tract.

5 More particularly, the invention relates to an osmotic device comprising a wall formed of a semi-permeable pH sensitive composition that surrounds a compartment containing a drug, with a passageway through the wall connecting the exterior of the device with the compartment. The device delivers the drug at a controlled rate in the region of the gastrointestinal tract having a pH of less than 3.5, and the device self-destructs and
10 releases all its drug in the region of the gastrointestinal tract having a pH greater than 3.5, thereby providing total availability for drug absorption. U. S. Patent Nos. 5,609, 590 and 5, 358,502 disclose an osmotic bursting device for dispensing a beneficial agent to an aqueous environment. The device comprises a beneficial agent and osmagent surrounded at least in part by a semi-permeable membrane. The beneficial agent may also function as
15 the osmagent. The semi-permeable membrane is permeable to water and substantially impermeable to the beneficial agent and osmagent. A trigger means is attached to the semi-permeable membrane (e. g. , joins two capsule halves). The trigger means is activated by a pH of from 3 to 9 and triggers the eventual, but sudden, delivery of the beneficial agent. These devices enable the pH-triggered release of the beneficial agent
20 core as a bolus by osmotic bursting.

The compounds described herein may be formulated based on the invention described in U. S. Patent No. 5,316, 774 which discloses a composition for the controlled release of an active substance comprising a polymeric particle matrix, where each particle defines a
25 network of internal pores. The active substance is entrapped within the pore network together with a blocking agent having physical and chemical characteristics selected to modify the release rate of the active substance from the internal pore network. In one embodiment, drugs may be selectively delivered to the intestines using an enteric material as the blocking agent. The enteric material remains intact in the stomach but
30 degrades under the pH conditions of the intestines. In another embodiment, the sustained release formulation employs a blocking agent, which remains stable under the expected

conditions of the environment to which the active substance is to be released. The use of pH-sensitive materials alone to achieve site-specific delivery is difficult because of leaking of the beneficial agent prior to the release site or desired delivery time and it is difficult to achieve long time lags before release of the active ingredient after exposure to high pH (because of rapid dissolution or degradation of the pH-sensitive materials).

The agents may also be formulated in a hybrid system which combines pH-sensitive materials and osmotic delivery systems. These hybrid devices provide delayed initiation of sustained-release of the beneficial agent. In one device a pH-sensitive matrix or coating dissolves releasing osmotic devices that provide sustained release of the beneficial agent see U. S. Patent Nos. 4,578, 075, 4,681, 583, and 4,851, 231. A second device consists of a semipermeable coating made of a polymer blend of an insoluble and a pH-sensitive material. As the pH increases, the permeability of the coating increases, increasing the rate of release of beneficial agent see U. S. Patent Nos. 4,096, 238, 4, 503,030, 4, 522, 625, and 4,587, 117.

The compounds described herein may be formulated in terpolymers according to U. S. Patent No. 5,484, 610 which discloses terpolymers which are sensitive to pH and temperature which are useful carriers for conducting bioactive agents through the gastric juices of the stomach in a protected form. The terpolymers swell at the higher physiologic pH of the intestinal tract causing release of the bioactive agents into the intestine. The terpolymers are linear and are made up of 35 to 99 wt % of a temperature sensitive component, which imparts to the terpolymer LCST (lower critical solution temperature) properties below body temperatures, 1 to 30 wt % of a pH sensitive component having a pKa in the range of from 2 to 8 which functions through ionization or deionization of carboxylic acid groups to prevent the bioactive agent from being lost at low pH but allows bioactive agent release at physiological pH of about 7.4 and a hydrophobic component which stabilizes the LCST below body temperatures and compensates for bioactive agent effects on the terpolymers. The terpolymers provide for safe bioactive agent loading, a simple procedure for dosage form fabrication and the terpolymer functions as a protective carrier in the acidic environment of the stomach and also

protects the bioactive agents from digestive enzymes until the bioactive agent is released in the intestinal tract.

The compounds described herein may be formulated in pH sensitive polymers according to those described in U. S. Patent No. 6,103, 865. U. S. Patent No. 6,103, 865 discloses pH-sensitive polymers containing sulfonamide groups, which can be changed in physical properties, such as swellability and solubility, depending on pH and which can be applied for a drug-delivery system, bio-material, sensor, and the like, and a preparation method therefore. The pH-sensitive polymers are prepared by introduction of sulfonamide groups, various in pKa, to hydrophilic groups of polymers either through coupling to the hydrophilic groups of polymers, such as acrylamide, N, N- dimethylacrylamide, acrylic acid, N-isopropylacrylamide and the like or copolymerization with other polymerizable monomers. These pH-sensitive polymers may have a structure of linear polymer, grafted copolymer, hydrogel or interpenetrating network polymer.

The compounds described herein may be formulated according U. S. Patent No. 5, 656, 292 which discloses a composition for pH dependent or pH regulated controlled release of active ingredients especially drugs. The composition consists of a compactable mixture of the active ingredient and starch molecules substituted with acetate and dicarboxylate residues. The preferred dicarboxylate acid is succinate. The average substitution degree of the acetate residue is at least 1 and 0. 2-1. 2 for the dicarboxylate residue. The starch molecules can have the acetate and dicarboxylate residues attached to the same starch molecule backbone or attached to separate starch molecule backbones. The present invention also discloses methods for preparing said starch acetate dicarboxylates by transesterification or mixing of starch acetates and starch dicarboxylates respectively.

The compounds described herein may be formulated according to the methods described in U. S. Patent Nos. 5,554, 147,5, 788, 687, and 6,306, 422 which disclose a method for the controlled release of a biologically active agent wherein the agent is released from a hydrophobic, pH-sensitive polymer matrix. The polymer matrix swells when the environment reaches pH 8.5, releasing the active agent. A polymer of hydrophobic and

weakly acidic comonomers is disclosed for use in the controlled release system. Also disclosed is a specific embodiment in which the controlled release system may be used. The pH-sensitive polymer is coated onto a latex catheter used in ureteral catheterization. A ureteral catheter coated with a pH-sensitive polymer having an antibiotic or urease inhibitor trapped within its matrix will release the active agent when exposed to high pH urine.

The compounds described herein may be formulated in/with bioadhesive polymers according to US Patent No. 6,365, 187. Bioadhesive polymers in the form of, or as a coating on, microcapsules containing drugs or bioactive substances which may serve for therapeutic, or diagnostic purposes in diseases of the gastrointestinal tract, are described in US6365187. The polymeric microspheres all have a bioadhesive force of at least 11 mN/cm² (110 N/m²) Techniques for the fabrication of bioadhesive microspheres, as well as a method for measuring bioadhesive forces between microspheres and selected segments of the gastrointestinal tract in vitro are also described. This quantitative method provides a means to establish a correlation between the chemical nature, the surface morphology and the dimensions of drug-loaded microspheres on one hand and bioadhesive forces on the other, allowing the screening of the most promising materials from a relatively large group of natural and synthetic polymers which, from theoretical consideration, should be used for making bioadhesive microspheres. Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including intraocular), intranasal (including using a cannula), or by other routes. The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, granules, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g. WO 97/11682) via a liposomal formulation (see, e.g., EP 736299, WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886 or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The agents can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al. 2004, Nature Reviews Drug Discovery 3:115)). The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisobornide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal administration. The agents can be administered in the form a suppository or by other vaginal or rectal means. The agents can be administered in a transmembrane formulation as described in WO 90/07923. The agents can be administered non-invasively via the dehydrated particles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug formulation as described in WO 02/49621. The agents can be administered intranasally using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral

injection are described in WO 00/62759. The agents can be administered using the casein formulation described in U. S. 20030206939 and WO 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

5 The agents, alone or in combination with other suitable components, can be administered by pulmonary route utilizing several techniques including but not limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs) and aerosol inhalation. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs)) can also be
10 used in intranasal applications. Aerosol formulations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluoroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluorocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and
15 the like. Pulmonary formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion. Pulmonary formulations may also include surfactants which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, e.g., a C8-C16 fatty acid salt, a bile salt, a
25 phospholipid, or alkyl saccharide are advantageous in that some of them also reportedly enhance absorption of the compound in the formulation. Also suitable in the invention are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers which can be added to dry powder
30 formulations of the present invention include those described in U.S. 6,632,456. WO 02/080884 describes new methods for the surface modification of powders. Aerosol

formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 01/78694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S.

20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO

5 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885. Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are described in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S.
10 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a liposomal based formulation that can be administered via aerosol or other means. Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824.

15 Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American
20 Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

25 The agent can be fused to immunoglobulins or albumin, or incorporated into a liposome to improve half-life. The agent can also be conjugated to polyethylene glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2: 214-221 and the references therein. The agent can be
30 administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences

International). The agents can be delivered transmucosally (i.e. across a mucosal surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means

Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, 1995.

Methods to increase chemical and/or physical stability of the agents the described herein are found in WO 00/04880, and WO 97/04796 and the references cited therein.

Methods to increase bioavailability of the agents described herein are found in U.S. 20030198619, WO 01/49268, WO 00/32172, and WO 02/064166. Glycyrrhizinate can also be used as an absorption enhancer (see, e.g., EP397447). WO 03/004062 discusses

Ulex europaeus I (UEAI) and UEAI mimetics which may be used to target the agents to the GI tract.

Kits

The compounds and pharmaceutical formulations described herein may be contained in a kit. The kit may include single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation. Thus, the kits can comprise: a) a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier, vehicle or diluent; and b) a container or packaging. The kits may optionally comprise instructions describing a method of using the pharmaceutical compositions in one or more of the methods described herein (e.g. preventing or treating one or more of the diseases and disorders described herein). The kit may optionally comprise a second pharmaceutical composition comprising one or more additional agents described herein for cotherapy use, a pharmaceutically acceptable carrier, vehicle or diluent. The pharmaceutical composition comprising the compound described herein and the second pharmaceutical composition contained in the kit may be optionally combined in the same pharmaceutical composition.

A kit includes a container or packaging for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. It is feasible that more than one container can be

used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

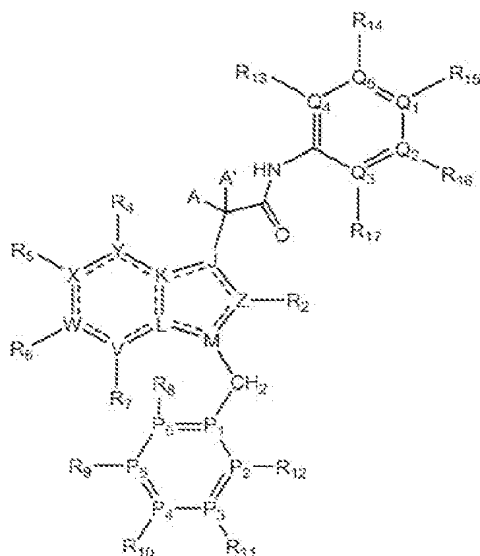
An example of a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It maybe desirable to provide a written memory aid containing information and/or instructions for the physician, pharmacist or subject regarding when the medication is to be taken. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. When the kit contains separate compositions, a daily dose of one or more compositions of the kit can consist of one tablet or capsule while a daily dose of another one or more compositions of the kit can consist of several tablets or capsules. A kit can take the form of a dispenser designed to dispense the daily doses one at a time in the order of their intended use. The dispenser can be equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that have been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the

date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

A number of embodiments have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the
5 invention.

1. A compound having Formula A or a pharmaceutically acceptable salt thereof



5

Formula A

wherein:

each of V, W, X, Y, Z, J, K, L, and M are independently N or C;

- 10 each of P₁, P₂, P₃, P₄, P₅ and P₆ are independently N or C;

each of Q₁, Q₂, Q₃, Q₄, and Q₅ are independently N or C;

- 15 A and A' are independently: hydroxyl or an optionally independently substituted C1 to C3 alkoxy or A and A' taken together are =O, =N(OH) or =NOCH₃ or A and A' together with the carbon to which they are attached form a cyclic ketal containing a total of 4 or 5 carbon atoms which can be optionally independently substituted;

|||

indicates a double or single bond;

R₂ is halogen, hydroxyl, -NO₂, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C1-C5 alkoxy, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, -CN, -C(O)OH, an optionally independently substituted cyclopropyl, -C(O)NR_{2a}R_{2b}, or -

5 NR_{2a}R_{2b}, wherein R_{2a} and R_{2b} are independently H or C1-C3 alkyl;

each of R₄, R₅, R₆ and R₇, when bonded to C, is independently: H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b,
10 wherein R_a and R_b are independently H, an optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

each of R₄, R₅, R₆ and R₇, when bonded to N, is missing;

each of R₈, R₉, R₁₀, R₁₁ and R₁₂, when bonded to C, is independently: H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, an optionally independently substituted C1-C5 alkyl, an
15 optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b, wherein R_a and R_b are independently H, an optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

20 each of R₈, R₉, R₁₀, R₁₁ and R₁₂, when bonded to N, is missing;

when Q₅ is C, R₁₄ is selected from H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b, wherein R_a and R_b are
25 independently H, an optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

when Q₅ is N, R₁₄ is missing;

when Q_2 is C, R_{16} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are
5 independently H, optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

when Q_2 is N, R_{16} is missing;

when Q_1 is C, R_{15} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted
10 C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

when Q_1 is N, R_{15} is missing;

15 when Q_4 is C, R_{13} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, optionally independently substituted C1-C6 alkyl, or an optionally
20 independently substituted C3-C6 cycloalkyl;

when Q_4 is N, R_{13} is missing;

when Q_3 is C, R_{17} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally
25 independently substituted C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

and

when Q₃ is N, R₁₇ is missing,

with the following provisos:

- 5 when: V, W, X, Y, Z, J, K and L are C; M is N; P₁, P₂, P₃, P₄, P₅ and P₆ are C; Q₁, Q₂, Q₃, Q₄, and Q₅ are C; R₂ is methyl; and A and A' taken together are =O, R₁₅ is not C(O)NH₂ and R₁₆ is not Cl;

- when: V, W, X, Y, Z, J, K and L are C; M is N; P₁, P₂, P₃, P₄, P₅ and P₆ are C; Q₁, Q₂, Q₃, Q₄, and Q₅ are C; R₂ is methyl; and A and A' taken together are =O, R₈, R₉, R₁₀, R₁₁, and
10 R₁₂ are not all H and R₁₃ and R₁₇ are not both methyl; and

when: V, W, X, Y, Z, J, K and L are C; M is N; P₁, P₂, P₃, P₄, P₅ and P₆ are C; Q₁, Q₂, Q₃, Q₄, and Q₅ are C; R₂ is methyl; and A and A' taken together are =O, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇ are not all H.

2. The compound of claim 1 wherein each of V, W, X, Y, Z, J, K and L are C and M
15 is N.

3. The compound of claim 1 wherein: a) one, none, one or two of V, W, X, Y, Z, J, K, L are N and the rest are C; and b) M is N or C.

- 20 4. The compound of claim 3 wherein: a) two of V, W, X, Y, Z, J, K, L are N and the rest are C; and b) M is N or C.

5. The compound of claim 3 wherein: a) one of V, W, X, Y, Z, J, K, L are N and the rest are C; and b) M is N or C.

25

6. The compound of claim 3 wherein: a) V, W, X, Y, Z, J, K, L are C; and b) M is N or C.

7. The compound of claim 3 wherein: a) W, X, Y, Z, J, K, L are C; b) M is N or C; and c) V is N.

5 8. The compound of claim 3 wherein: a) V, W, Y, Z, J, K, L are C; b) M is N or C; and c) X is N.

9 The compound of any of claims 1-8 wherein: none, one or two of P₁, P₂, P₃, P₄, P₅ and P₆ are independently N and the rest are C.

10

10. The compound of claim 9 wherein two of P₁, P₂, P₃, P₄, P₅ and P₆ are N and the rest are C.

15

11. The compound of claim 9 wherein one of P₁, P₂, P₃, P₄, P₅ and P₆ is N and the rest are C.

12. The compound of claim 9 wherein P₁, P₂, P₃, P₄, P₅ and P₆ are C.

13. The compound of any of claims 1 – 12 wherein M is N.

20

14. The compound of any of claims 1 – 12 wherein M is C.

15. The compound of any of claims 1 – 14 wherein Q₄ is N and Q₁, Q₂, Q₃ and Q₅ are C.

25

16. The compound of any of claims 1 – 14 wherein Q₅ is N and Q₁, Q₂, Q₃ and Q₄ are C.

17. The compound of any of claims 1 – 14 wherein Q₁ is N and Q₂, Q₃, Q₄ and Q₅ are C.

30

18. The compound of any of claims 1 – 14 wherein Q_4 and Q_1 are N and Q_2 , Q_3 and Q_5 are C.

19. The compound of any of claims 1 – 14 wherein Q_4 and Q_3 are N and Q_2 , Q_1 and
5 Q_5 are C.

20. The compound of any of claims 1 – 14 wherein Q_4 and Q_2 are N and Q_1 , Q_3 and Q_5 are C.

21. The compound of any of claims 1 – 14 wherein Q_4 and Q_5 are N and Q_2 , Q_3 and Q_1 are C.

22. The compound of any of claims 1 – 14 wherein Q_4 , Q_3 , and Q_1 are N and Q_5 and Q_2 are C.

15

23. The compound of any of claims 1 – 14 wherein Q_5 , Q_4 , Q_3 , Q_2 and Q_1 are C.

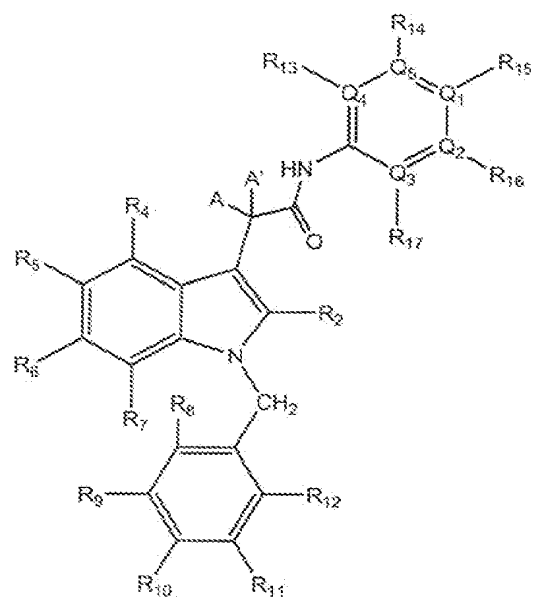
24. The compound of any of claims 1 – 14 wherein only one of Q_5 , Q_4 , Q_3 , Q_2 and Q_1 is N.

20

25. The compound of any of claims 1 – 14 wherein only two of Q_5 , Q_4 , Q_3 , Q_2 and Q_1 are N.

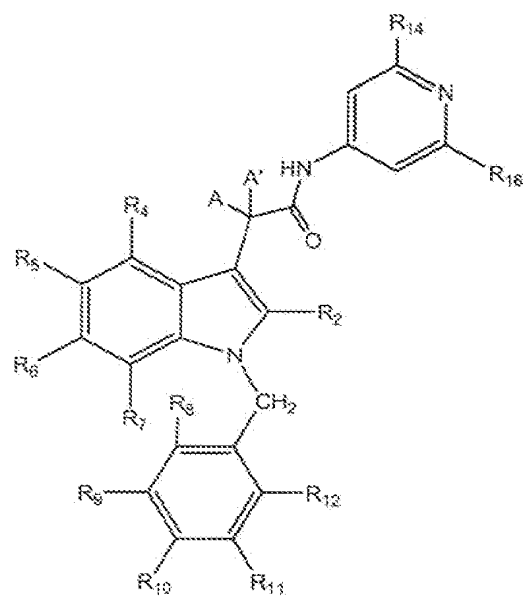
26. The compound of any of claims 1 – 14 wherein only three of Q_5 , Q_4 , Q_3 , Q_2 and
25 Q_1 are N.

27. The compound of claim 1 having the Formula A-1



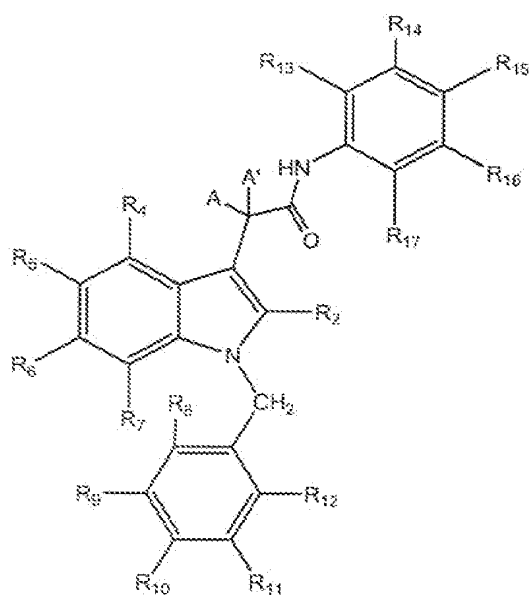
Formula A-1

28. The compound of claim 1 having Formula A-2



5 Formula A-2

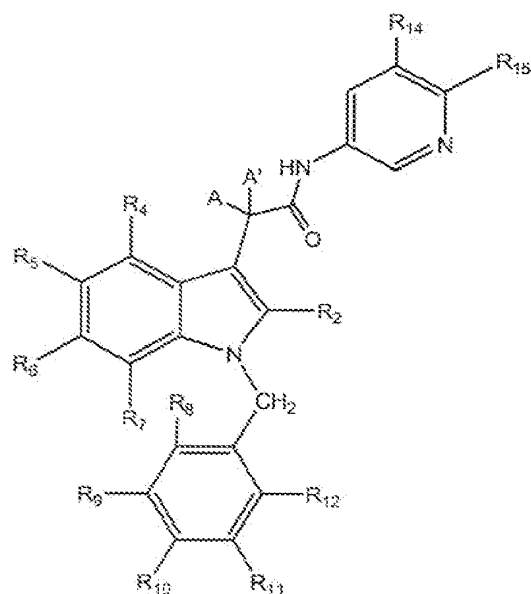
29. The compound of claim 1 having Formula A-3



Formula A-3

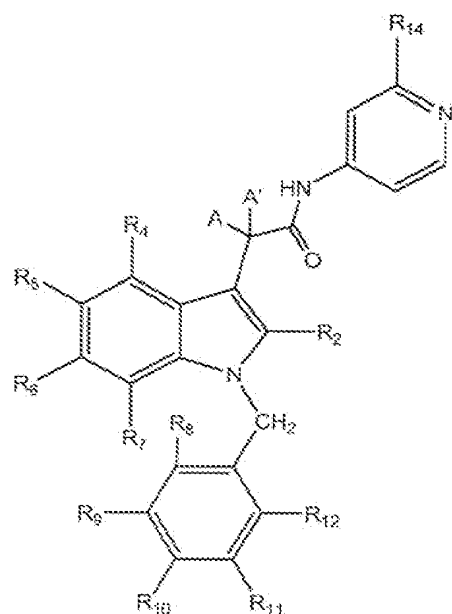
30. The compound of claim 1 having Formula A-4

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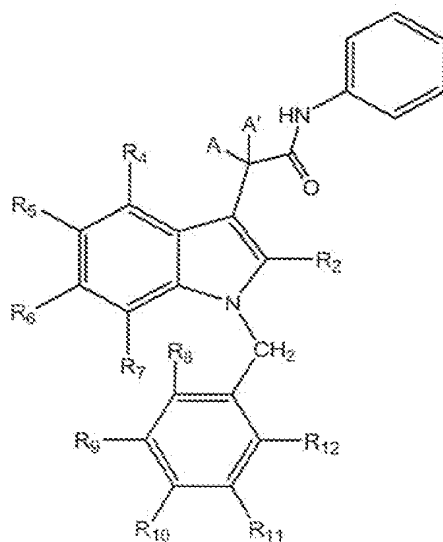
Formula A-4

31. The compound of claim 1 having Formula A-5



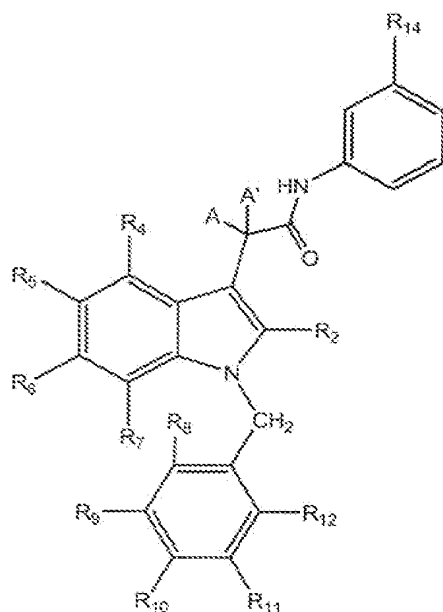
Formula A-5

32. The compound of claim 1 having Formula A-6



5 Formula A-6

33. The compound of claim 1 having Formula A-7



Formula A-7

34. The compound of any of any of claims 1-33 wherein A and A' are hydroxyl.

5

35. The compound of any of claims 1-33 wherein A and A' are C1 to C3 alkoxy.

36. The compound of any of claims 1-33 wherein A and A' taken together with the carbon to which they are attached form a cyclic ketal containing a total of 4 or 5 carbon atoms which can be optionally singly or multiply substituted with a methyl group.

10

37. The compound of claim 36 wherein wherein A and A' taken together with the carbon to which they are attached form a cyclic ketal containing a total of 4 carbon atoms which can be optionally singly or multiply substituted with a methyl group.

15

38. The compound of any of claims 1-33 wherein A and A' taken together are =N(OH);

39. The compound of any of claims 1-33 wherein A and A' taken together are =NOCH₃;

20

40. The compound of any of claims 1-33 wherein A and A' taken together are =O.
41. The compound of any of claims 1-33 wherein R₂ is selected from: hydroxyl,
5 optionally independently substituted C1-C3 alkyl, an optionally independently halogen substituted cyclopropyl, an optionally independently halogen substituted ethoxy and an optionally independently halogen substituted methoxy.
42. The compound of any of claims 1-41 wherein R₂ is an optionally independently halogen substituted C1-C3 alkyl or cyclopropyl.
- 10 43. The compound of any of claims 1-42 wherein R₂ is methyl.
44. The compound of any of claims 1-41 wherein R₂ is a C1-C3 alkyl or cyclopropyl.
45. The compound of any of claims 1-44 wherein one or two of R₈, R₉, R₁₀, R₁₁ and R₁₂ are halogen and the rest are H.
46. The compound of any of claims 1-44 wherein one or two of R₈, R₉, R₁₀, R₁₁ and
15 R₁₂ are Cl or F and the rest are H.
47. The compound of any of claims 1-46 wherein R₁₀ is halogen.
48. The compound of any of claims 1-47 wherein one of R₈ and R₁₂ is halogen and the other is H.
49. The compound of any of claims 1-47 wherein R₁₀ is Cl or F and R₈, R₉, R₁₁ and
20 R₁₂ are H.
50. The compound of any of claims 1-47 wherein R₁₀ is Cl or F, R₈ is Cl or F; and R₉, R₁₁ and R₁₂ are H.
51. The compound of any of claims 1-50 wherein R₄ and R₇ are H.
52. The compound of any of claims 1-51 wherein R₆ is H.

53. The compound of any of claims 1-52 wherein R_5 is selected from: ethoxy, methoxy, ethyl, methyl, halogen and H.
54. The compound of claim 53 wherein R_5 is selected from: methoxy, ethyl, methyl and H.
- 5 55. The compound of claim 53 wherein R_5 is selected from: methoxy and methyl and H.
56. The compound of claim 53 wherein R_5 is methoxy.
57. The compound of claim 53 wherein R_5 is methyl.
58. The compound of claim 53 wherein R_5 is H.
- 10 59. The compound of any of claims 1-58 wherein R_{14} is halogen or an optionally independently substituted methoxy and both R_{13} and R_{17} are H.
60. The compound of claim 59 wherein R_{14} is Cl.
61. The compound of claim 59 wherein R_{14} is F.
62. The compound of claim 59 wherein R_{14} is $-OCH_3$.
- 15 63. The compound of any of claims 1-62 wherein any unspecified substituent is selected from: halogen, optionally independently halogen substituted C1-C3 alkyl, optionally independently substituted C1-C3 alkoxy, hydroxy, cyano, nitro and amino.
64. The compound of any of claims 1-63 wherein any unspecified substituent is selected from: halogen, hydroxy, and C1-C3 alkyl.
- 20 65. The compound of any of claims 1 and 27-33 wherein A and A' are independently: hydroxyl or a C1 to C3 alkoxy or A and A' taken together are $=O$, $=N(OH)$ or $=NOCH_3$ or A and A' together with the carbon to which they are attached form a cyclic ketal

containing a total of 4 or 5 carbon atoms which can be optionally independently substituted with methyl.

66. The compound of any of claims 1 and 27-33 wherein R_2 is halogen, hydroxyl, -NO₂, a C1-C5 alkyl, a C1-C5 alkoxy, a C2-C5 alkenyl, a C2-C5 alkynyl, -CN, -C(O)OH, a
5 cyclopropyl, -C(O)NR_{2a}R_{2b}, or -NR_{2a}R_{2b}, wherein R_{2a} and R_{2b} are independently H or C1-C3 alkyl;

67. The compound of any of claims 1 and 27-33 wherein each of R₄, R₅, R₆ and R₇, when bonded to C, is independently: H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b,
10 wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl;

68. The compound of any of claims 1 and 27-33 wherein each of R₈, R₉, R₁₀, R₁₁ and R₁₂, when bonded to C, is independently: H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, -C(O)NR_aR_b, or -
15 NR_aR_b, wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl;

69. The compound of any of claims 1 and 27-33 wherein R₁₄ is selected from H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b, wherein R_a and R_b are independently H, a
20 C1-C6 alkyl, or a C3-C6 cycloalkyl.

70. The compound of any of claims 1 and 27-33 wherein R₁₅ is selected from H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b, wherein R_a and R_b are independently H,
25 a C1-C6 alkyl, or a C3-C6 cycloalkyl.

71. The compound of any of claims 1 and 27-33 wherein R₁₆ is selected from H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b, wherein R_a and R_b are independently H,
30 a C1-C6 alkyl, or a C3-C6 cycloalkyl.

72. The compound of any of claims 1 and 27-33 wherein R_{13} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl.

73. The compound of any of claims 1 and 27-33 wherein R_{17} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl.

74. The compound of any of claims 1-33 wherein R_2 is methyl; R_9 and R_{11} are H; R_{10} is Cl or F, R_8 is H, and R_{12} is Cl, H or F; R_4 , R_6 and R_7 are H; R_5 is methoxy, methyl or H; A and A' together are $=\text{O}$; R_{14} is H; R_{16} is Cl, F, or methoxy.

75. The compound of any of claims 1-33 wherein R_2 is methyl; R_9 and R_{11} are H; R_{10} is Cl or F, R_8 is H, and R_{12} is Cl, H or F; R_4 , R_6 and R_7 are H; R_5 is methoxy, methyl or H; A and A' together are $=\text{O}$ or an optionally methyl substituted cyclic ketal; R_{14} is H; R_{16} is Cl, F, or methoxy.

76. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any of claims 1-75 and a pharmaceutically acceptable carrier.

77. A method for treating pain comprising administering the pharmaceutical composition of claim 76 to a patient in need thereof.

78. The method of claim 77 wherein the pain is acute.

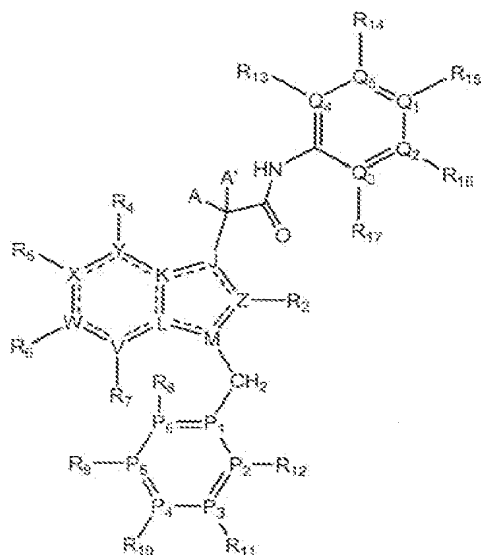
79. The method of claim 77 wherein the pain is chronic.

80. The method of claim 77 wherein the pain is neurogenic pain.

81. The method of claim 80 wherein the neurogenic pain is migraine.

82. The method of claim 77 wherein the pain is caused by inflammation.
83. The method of claim 82 wherein the inflammation is selected from: arthritis, osteoarthritis, spondylitis and rheumatoid arthritis.
84. The method of claim 82 wherein the inflammation is selected from Crohn's
5 disease and irritable bowel syndrome.
85. The method of claim 77 wherein the pain is neuropathic pain.
86. A method for treating anxiety comprising administering the pharmaceutical composition of claim 76 to a patient in need thereof.
87. A method for treating an eating disorder comprising administering the
10 pharmaceutical composition of claim 76 to a patient in need thereof.
88. The method of claim 87 wherein the patient is suffering from anorexia.
89. The method of claim 87 wherein the patient is suffering from bulimia.
90. A method for treating obesity comprising administering the pharmaceutical composition of claim 76 to a patient in need thereof.
- 15 91. A method for reducing food intake comprising administering the pharmaceutical composition of claim 76 to a patient in need thereof.
92. A method for reducing intraocular pressure comprising administering the pharmaceutical composition of claim 76 to a patient in need thereof.
93. The method of claim 92 wherein the patient is suffering from glaucoma.
- 20 94. A method for treating a cardiovascular disorder comprising administering the pharmaceutical composition of claim 76 to a patient in need thereof.

95. A method for treating depression comprising administering the pharmaceutical composition of claim 76 to a patient in need thereof.
96. A method for treating an inflammatory disorder comprising administering the pharmaceutical composition of claim 76 to a patient in need thereof.
- 5 97. The method of claim 96 wherein the inflammatory disorder is selected from: allergy, respiratory inflammation, inflammation of the skin and gastrointestinal inflammation.
98. The method of claim 97 wherein the respiratory inflammation is asthma.
99. The method of claim 97 wherein the gastrointestinal inflammation is Crohn's
10 disease.
100. The method of claim 97 wherein the gastrointestinal inflammation is inflammatory bowel disease.
101. A method of treating pain, an eating disorder, depression an inflammatory disorder, a cardiovascular disorder, elevated intraocular pressure or anxiety comprising
15 administering a compound having Formula A or a pharmaceutically acceptable salt thereof



Formula A

5 wherein:

each of V, W, X, Y, Z, J, K, L, and M are independently N or C;

each of P_1, P_2, P_3, P_4, P_5 and P_6 are independently N or C;

10 each of Q_1, Q_2, Q_3, Q_4 , and Q_5 are independently N or C;

A and A' are independently: hydroxyl or an optionally independently substituted C1 to C3 alkoxy or A and A' taken together are =O, =N(OH) or =NOCH₃ or A and A' together with the carbon to which they are attached form a cyclic ketal containing a total of 4 or 5 carbon atoms which can be optionally independently substituted;

||||| indicates a double or single bond;

R₂ is H, halogen, hydroxyl, -NO₂, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C1-C5 alkoxy, an optionally independently

substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, -CN, -C(O)OH, an optionally independently substituted cyclopropyl, -C(O)NR_{2a}R_{2b}, or -NR_{2a}R_{2b}, wherein R_{2a} and R_{2b} are independently H or C1-C3 alkyl;

5 each of R₄, R₅, R₆ and R₇, when bonded to C, is independently: H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b, wherein R_a and R_b are independently H, an optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

10 each of R₄, R₅, R₆ and R₇, when bonded to N, is missing;

each of R₈, R₉, R₁₀, R₁₁ and R₁₂, when bonded to C, is independently: H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b, wherein R_a and R_b are independently H, an optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

15

each of R₈, R₉, R₁₀, R₁₁ and R₁₂, when bonded to N, is missing;

when Q₅ is C, R₁₄ is selected from H, a halogen, -NO₂, -CN, -C(O)OH, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, -C(O)NR_aR_b, or -NR_aR_b, wherein R_a and R_b are independently H, an optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

20

25 when Q₅ is N, R₁₄ is missing;

when Q_2 is C, R_{16} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are
5 independently H, optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

when Q_2 is N, R_{16} is missing;

when Q_1 is C, R_{15} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted
10 C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

when Q_1 is N, R_{15} is missing;

15 when Q_4 is C, R_{13} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally independently substituted C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, optionally independently substituted C1-C6 alkyl, or an optionally
20 independently substituted C3-C6 cycloalkyl;

when Q_4 is N, R_{13} is missing;

when Q_3 is C, R_{17} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, an optionally independently substituted C1-C5 alkyl, an optionally independently substituted C2-C5 alkenyl, an optionally independently substituted C2-C5 alkynyl, an optionally
25 independently substituted C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, optionally independently substituted C1-C6 alkyl, or an optionally independently substituted C3-C6 cycloalkyl;

and

when Q_3 is N, R_{17} is missing.

102. The method of claim 101 wherein each of V, W, X, Y, Z, J, K and L are C and M
5 is N.

103. The method of claim 101 wherein: a) one, none, one or two of V, W, X, Y, Z, J, K, L are N and the rest are C; and b) M is N or C.

104. The method of claim 103 wherein: a) two of V, W, X, Y, Z, J, K, L are N and the
10 rest are C; and b) M is N or C.

105. The method of claim 103 wherein: a) one of V, W, X, Y, Z, J, K, L are N and the
rest are C; and b) M is N or C.

15

106. The method of claim 103 wherein: a) V, W, X, Y, Z, J, K, L are C; and b) M is N
or C.

107. The method of claim 103 wherein: a) W, X, Y, Z, J, K, L are C; b) M is N or C;
20 and c) V is N.

108. The method of claim 103 wherein: a) V, W, Y, Z, J, K, L are C; b) M is N or C;
and c) X is N.

25 109 The method of any of claims 101-108 wherein: none, one or two of P_1 , P_2 , P_3 , P_4 ,
 P_5 and P_6 are independently N and the rest are C.

110. The method of claim 109 wherein two of P_1 , P_2 , P_3 , P_4 , P_5 and P_6 are N and the
rest are C.

30

111. The method of claim 109 wherein one of P₁, P₂, P₃, P₄, P₅ and P₆ is N and the rest are C.

112. The method of claim 109 wherein P₁, P₂, P₃, P₄, P₅ and P₆ are C.

5

113. The method of any of claims 101 – 112 wherein M is N.

114. The method of any of claims 101 – 112 wherein M is C.

10 115. The method of any of claims 101 – 114 wherein Q₄ is N and Q₁, Q₂, Q₃ and Q₅ are C.

116. The method of any of claims 101 – 114 wherein Q₅ is N and Q₁, Q₂, Q₃ and Q₄ are C.

15

117. The method of any of claims 101 – 114 wherein Q₁ is N and Q₂, Q₃, Q₄ and Q₅ are C.

118. The method of any of claims 101 – 114 wherein Q₄ and Q₁ are N and Q₂, Q₃ and Q₅ are C.

20

119. The method of any of claims 101 – 114 wherein Q₄ and Q₃ are N and Q₂, Q₁ and Q₅ are C.

25 120. The method of any of claims 101 – 114 wherein Q₄ and Q₂ are N and Q₁, Q₃ and Q₅ are C.

121. The method of any of claims 101 – 114 wherein Q₄ and Q₅ are N and Q₂, Q₃ and Q₁ are C.

30

122. The method of any of claims 101 – 114 wherein Q₄, Q₃, and Q₁ are N and Q₅ and Q₂ are C.

123. The method of any of claims 101 – 114 wherein Q₅, Q₄, Q₃, Q₂ and Q₁ are C.

5

124. The method of any of claims 101 – 114 wherein one of Q₅, Q₄, Q₃, Q₂ and Q₁ is N.

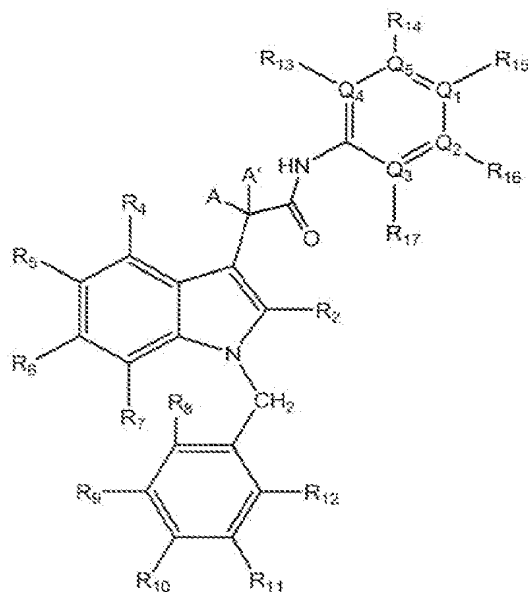
125. The method of any of claims 101 – 114 wherein two of Q₅, Q₄, Q₃, Q₂ and Q₁ are N.

10

126. The method of any of claims 101 – 114 wherein three of Q₅, Q₄, Q₃, Q₂ and Q₁ are N.

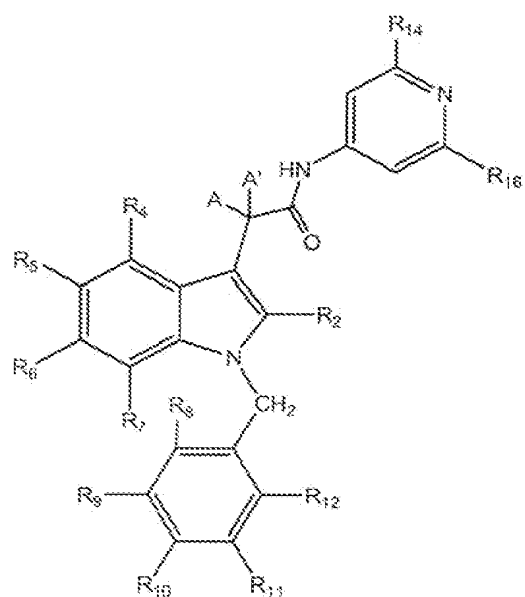
127. The method of claim 101 wherein the compound has Formula A-1

15



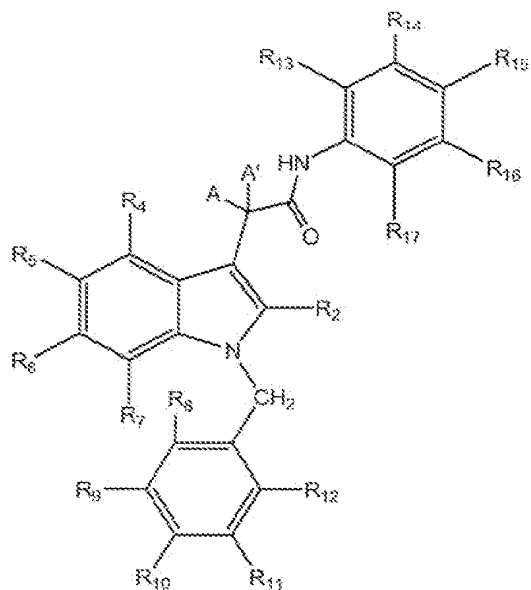
Formula A-1

128. The method of claim 101 wherein the compound has Formula A-2



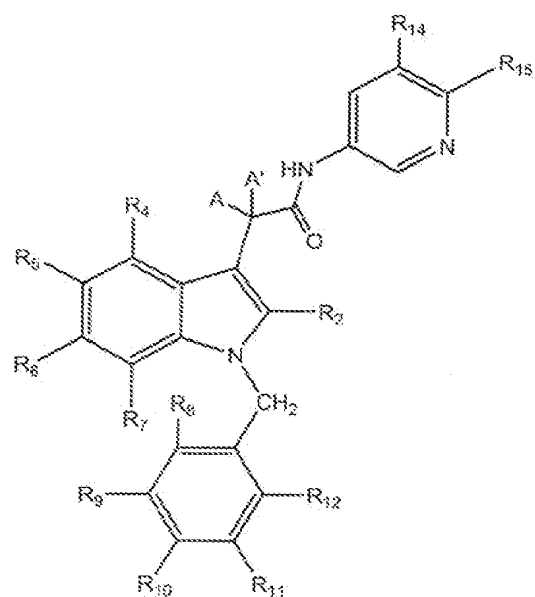
Formula A-2

129. The method of claim 101 wherein the compound has Formula A-3.



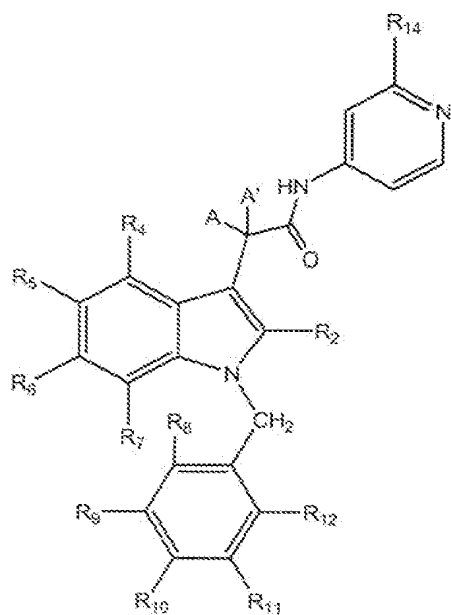
Formula A-3

130. The method of claim 101 wherein the compound has Formula A-4



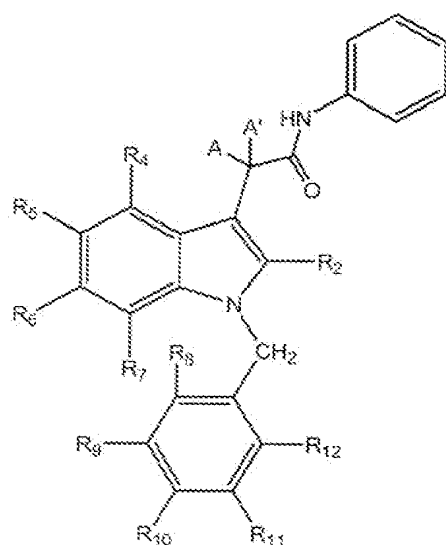
Formula A-4

131. The method of claim 101 wherein the compound has Formula A-5



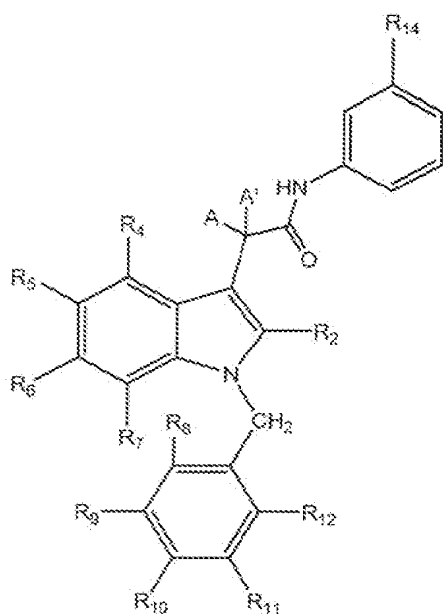
5 Formula A-5

132. The method of claim 101 wherein the compound has Formula A-6



Formula A-6

133. The method of claim 101 wherein the compound has Formula A-7



5 Formula A-7

134. The method of any of any of claims 101-133 wherein A and A' are hydroxyl.

135. The method of any of claims 101-133 wherein A and A' are C1 to C3 alkoxy.

136. The method of any of claims 101-133 wherein A and A' taken together with the carbon to which they are attached form a cyclic ketal containing a total of 4 or 5 carbon atoms which can be optionally singly or multiply substituted with a methyl group.

5 137. The method of claim 136 wherein A and A' taken together with the carbon to which they are attached form a cyclic ketal containing a total of 4 carbon atoms which can be optionally singly or multiply substituted with a methyl group.

138. The method of any of claims 101-133 wherein A and A' taken together are
10 =N(OH);

139. The method of any of claims 101-133 wherein A and A' taken together are
=NOCH₃;

15 140. The method of any of claims 101-133 wherein A and A' taken together are =O.

141. The method of any of claims 101-133 wherein R₂ is selected from: H, hydroxyl, optionally independently substituted C1-C3 alkyl, an optionally independently halogen substituted cyclopropyl, an optionally independently halogen substituted ethoxy and an
20 optionally independently halogen substituted methoxy.

142. The method of any of claims 101-141 wherein R₂ is H, an optionally independently halogen substituted C1-C3 alkyl or cyclopropyl.

143. The method of any of claims 101-142 wherein R₂ is H.

144. The method of any of claims 101-141 wherein R₂ is H, a C1-C3 alkyl or
25 cyclopropyl

145. The method of any of claims 101-144 wherein one or two of R₈, R₉, R₁₀, R₁₁ and R₁₂ are halogen and the rest are H.

146. The method of any of claims 101-144 wherein one or two of R_8 , R_9 , R_{10} , R_{11} and R_{12} are Cl or F and the rest are H.
147. The method of any of claims 101-146 wherein R_{10} is halogen.
148. The method of any of claims 101-147 wherein one of R_8 and R_{12} is halogen and
5 the other is H.
149. The method of any of claims 101-147 wherein R_{10} is Cl or F and R_8 , R_9 , R_{11} and R_{12} are H.
150. The method of any of claims 101-147 wherein R_{10} is Cl or F, R_8 is Cl or F, and R_9 , R_{11} and R_{12} are H.
- 10 151. The method of any of claims 101-150 wherein R_4 and R_7 are H.
152. The method of any of claims 101-141 wherein R_6 is H.
153. The method of any of claims 101-152 wherein R_5 is selected from: ethoxy, methoxy, ethyl, methyl, halogen and H.
154. The method of claim 153 wherein R_5 is selected from: methoxy, ethyl, methyl and
15 H.
155. The method of claim 153 wherein R_5 is selected from: methoxy and methyl and H.
156. The method of claim 153 wherein R_5 is methoxy.
157. The method of claim 153 wherein R_5 is methyl.
- 20 158. The method of claim 153 wherein R_5 is H.
159. The method of any of claims 101-158 wherein R_{14} is halogen or an optionally independently substituted methoxy and both R_{13} and R_{17} are H.

160. The method of claim 159 wherein R_{14} is Cl.
161. The method of claim 159 wherein R_{14} is F.
162. The method of claim 159 wherein R_{14} is $-OCH_3$.
163. The method of any of claims 101-162 wherein any unspecified substituent is
5 selected from: halogen, optionally independently halogen substituted C1-C3 alkyl,
optionally independently substituted C1-C3 alkoxy, hydroxy, cyano, nitro and amino.
164. The method of any of claims 101-163 wherein any unspecified substituent is
selected from: halogen, hydroxy, and C1-C3 alkyl.
165. The method of claim 101 wherein A and A' are independently: hydroxyl or a C1
10 to C3 alkoxy or A and A' taken together are $=O$, $=N(OH)$ or $=NOCH_3$ or A and A'
together with the carbon to which they are attached form a cyclic ketal containing a total
of 4 or 5 carbon atoms which can be optionally independently substituted with methyl.
166. The method of claim 101 wherein R_2 is halogen, hydroxyl, $-NO_2$, a C1-C5 alkyl, a
15 C1-C5 alkoxy, a C2-C5 alkenyl, a C2-C5 alkynyl, $-CN$, $-C(O)OH$, a cyclopropyl, $-$
 $C(O)NR_{2a}R_{2b}$, or $-NR_{2a}R_{2b}$, wherein R_{2a} and R_{2b} are independently H or C1-C3 alkyl;
167. The method of claim 101 wherein each of R_4 , R_5 , R_6 and R_7 , when bonded to C, is
independently: H, a halogen, $-NO_2$, $-CN$, $-C(O)OH$, hydroxyl, a C1-C5 alkyl, a C2-C5
alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-C(O)NR_aR_b$, or $-NR_aR_b$, wherein R_a and R_b are
20 independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl;
168. The method of claim 101 wherein each of R_8 , R_9 , R_{10} , R_{11} and R_{12} , when bonded
to C, is independently: H, a halogen, $-NO_2$, $-CN$, $-C(O)OH$, hydroxyl, a C1-C5 alkyl, a
C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-C(O)NR_aR_b$, or $-NR_aR_b$, wherein R_a
25 and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl;

169. The method of claim 101 wherein R_{14} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl.

5

170. The method of claim 101 wherein R_{15} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl.

10

171. The method of claim 101 wherein R_{16} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl.

15

172. The method of claim 101 wherein R_{13} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl.

20

173. The method of claim 101 wherein R_{17} is selected from H, a halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, hydroxyl, a C1-C5 alkyl, a C2-C5 alkenyl, a C2-C5 alkynyl, a C1-C5 alkoxy, $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, or $-\text{NR}_a\text{R}_b$, wherein R_a and R_b are independently H, a C1-C6 alkyl, or a C3-C6 cycloalkyl.

25 174. The method of any of claims 101-133 wherein R_2 is H, methyl; R_9 and R_{11} are H; R_{10} is Cl or F, R_8 is H, and R_{12} is Cl, H or F; R_4 , R_6 and R_7 are H; R_5 is methoxy, methyl or H; A and A' together are =O; R_{14} is H; R_{16} is Cl, F, or methoxy.

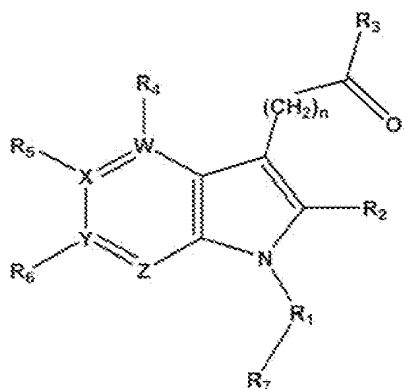
175. The method of any of claims 101-313 wherein R_2 is H, methyl; R_9 and R_{11} are H; R_{10} is Cl or F, R_8 is H, and R_{12} is Cl, H or F; R_4 , R_6 and R_7 are H; R_5 is methoxy, methyl or

H; A and A' together are =O or an optionally methyl substituted cyclic ketal; R₁₄ is H; R₁₆ is Cl, F, or methoxy.

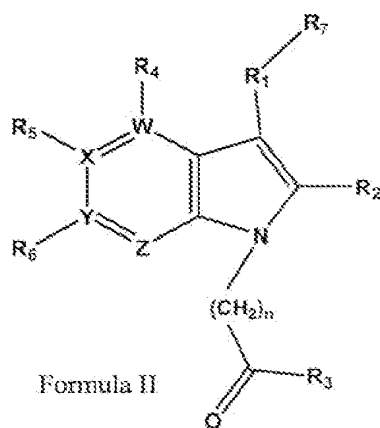
176. The method of any of claims 101-175 wherein the pain is acute.
177. The method of any of claims 101-175 wherein the pain is chronic.
- 5 178. The method of any of claims 101-175 wherein the pain is neurogenic pain.
179. The method of claim 178 wherein the neurogenic pain is migraine.
180. The method of any of claims 101-175 wherein the pain is caused by inflammation.
181. The method of claim 180 wherein the inflammation is selected from: arthritis,
10 osteoarthritis, spondylitis and rheumatoid arthritis.
182. The method of claim 180 wherein the inflammation is selected from Crohn's disease and irritable bowel syndrome.
183. The method of any of claims 101-175 wherein the pain is neuropathic pain.
184. The method of any of claims 101-175 wherein the method is a method for treating
15 an eating disorder
185. The method of any of claims 101-175 wherein the method is a method for treating an inflammatory disorder
186. The method of any of claims 101-175 wherein the method is a method for treating a cardiovascular disorder
- 20 187. The method of any of claims 101-175 wherein the method is a method for treating elevated intraocular pressure.
188. The method of any of claims 101-175 wherein the pain is acute.

189. The method of any of claims 101-175 wherein the pain is chronic.
190. The method of any of claims 101-175 wherein the pain is neurogenic pain.
191. The method of claim 190 wherein the neurogenic pain is migraine.
192. The method of any of claims 101-175 wherein the pain is caused by
5 inflammation.
193. The method of claim 192 wherein the inflammation is selected from: arthritis, osteoarthritis, spondylitis and rheumatoid arthritis.
194. The method of claim 192 wherein the inflammation is selected from Crohn's disease and irritable bowel syndrome.
- 10 195. The method of any of claims 101-175 wherein the pain is neuropathic pain.
196. The method of any of claims 101-175 which is a method for treating anxiety. 197.
197. The method of any of claims 101-175 which is a method for treating an eating disorder.

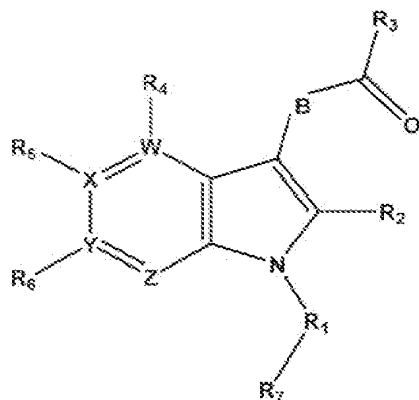
199. The method of claim 197 wherein the patient is suffering from anorexia.
200. The method of claim 197 wherein the patient is suffering from bulimia.
201. A compound having Formula I, Formula II or Formula III:



Formula I



Formula II



Formula III

wherein W, X, Y and Z are selected from C and N, provided that only one of W, X, Y and Z is N;


10 n = 0, 1, 2, 3, 4 and 5;


B is a 2 to 5 carbon chain, optionally containing at least one double bond;

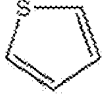
carbon in R₉ can be optionally, independently singly or multiply substituted with halogen, -OH, C2-C6 alkyl, C2-C6 alkoxy, -OCH₃, -CN, -CH₃, -NO₂, wherein any carbon in the substituent can be optionally, independently singly or multiply substituted with a halogen;

- 5 R₁₀ and R₁₁ are independently selected from H, C₁-C₅ alkyl, a cycloalkyl group, an aryl group, and a heteroaryl group, each optionally substituted at a substitutable position with C2-C4 alkyl, C2-C4 alkoxy, halogen, -NO₂, -CN, -OCF₃, -OH, -CH₃, -OCH₃ and -SCF₃, wherein any carbon in the substituent can be optionally, independently singly or multiply substituted with a halogen;
- 10 or R₁₀ and R₁₁ taken together with the N to which they are attached form a 3-7 membered ring, optionally independently singly or multiply substituted with: C2-C4 alkyl, C2-C4 alkoxy, halogen, -NO₂, -CN, -OCF₃, -OH, -CH₃, -OCH₃ and -SCF₃, wherein any carbon in the substituent can be optionally, independently singly or multiply substituted with a halogen.


15

202. The compound of claim 201 wherein R₇ is , optionally, independently singly or multiply substituted with R₈.

20 203. The compound of claim 201 wherein R₇ is , optionally, independently singly or multiply substituted with R₈.

204. The compound of claim 201 wherein R₇ is , optionally, independently singly or multiply substituted with one or more R₈.



205. The compound of claim 201 wherein R_7 is , optionally, independently singly or multiply substituted with one or more R_8 .

206. The compound of any of the forgoing claims wherein W, X, Y, and Z are all C.

5

207. The compound of any of the forgoing claims wherein n is 0.

208. The compound of any of claims 201-206 wherein n is 1.

10 209. The compound of any of claims 201-206 wherein n is 2.

210. The compound of any of the forgoing claims wherein R_3 is $-C(O)NHR_{10}$ or $-C(O)NR_{10}R_{11}$.

15 211. The compound of any claims 201-209 wherein R_3 is $-NHR_{10}$ or $-NR_{10}R_{11}$.

212. The compound of claim 210 wherein R_3 is $-C(O)NHR_{10}$.

213. The compound of claim 210 wherein R_3 is $-C(O)NR_{10}R_{11}$.

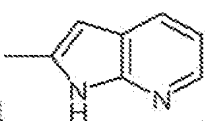
20

214. The compound of claim 211 wherein R_3 is $-NHR_{10}$.

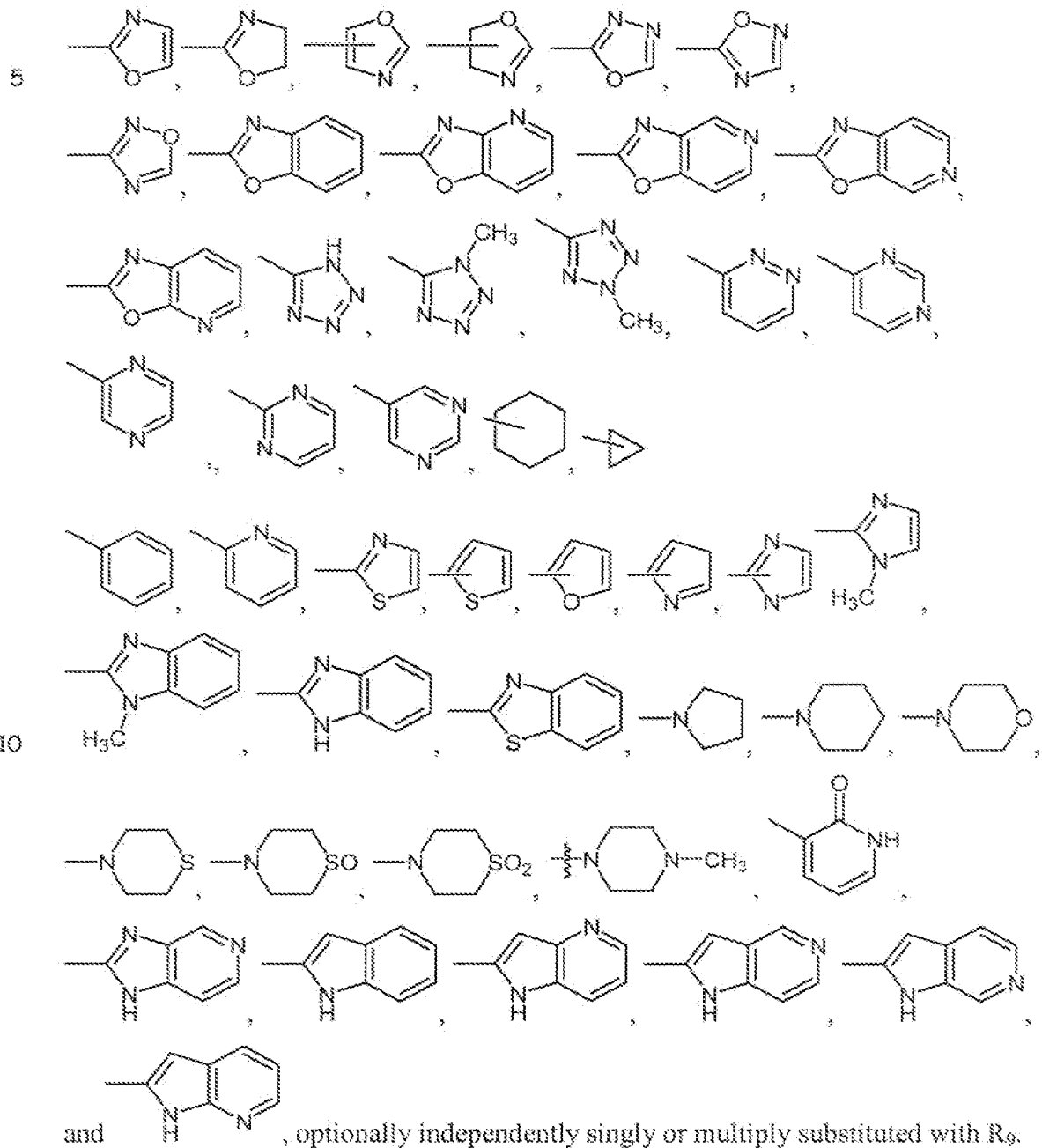
215. The compound of claim 211 wherein R_3 is $-NR_{10}R_{11}$.

25 216. The compound of any of claims 201-209 wherein R_3 is a monocyclic or bicyclic heteroaryl group, optionally independently substituted with one or more R_9 .

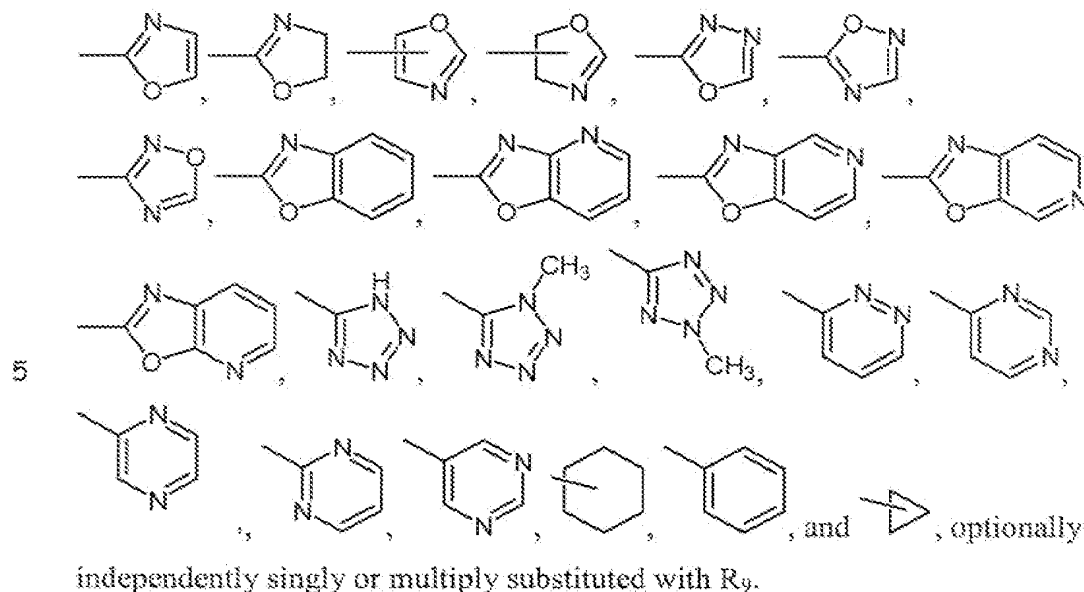
217. The compound of any of claims 201-209 wherein R_3 is a monocyclic or bicyclic cycloalkyl group, optionally independently substituted with one or more R_9 .

and , optionally independently singly or multiply substituted with one or more R₉.

222. The compound of any of claims 210-215 wherein R₁₀ is selected from:

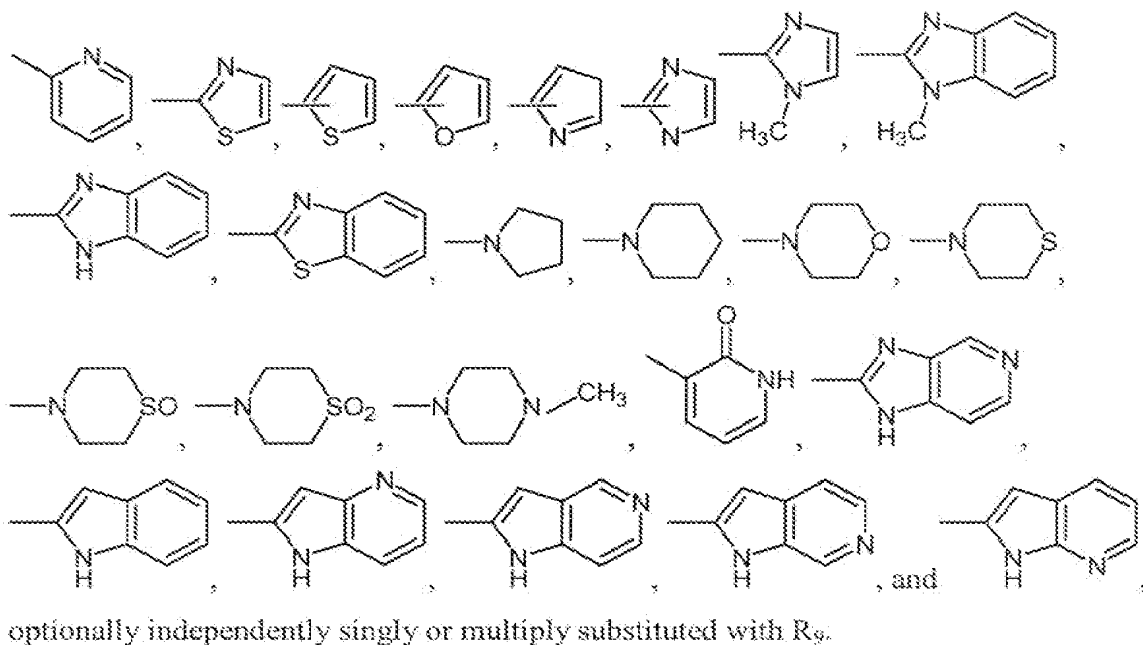


223. The compound of claim 222 wherein R_{10} is selected from:

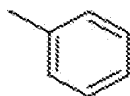


224. The compound of claim 222 wherein R_{10} is selected from:

10



225. The compound of any of claims 219, 221, 222 and 223 wherein R_{10} is not



226. The compound of any of claims 201-225 wherein R_1 is $-\text{CH}_2-$.

5 227. The compound of any claims 201-225 wherein R_1 is $-\text{C}(\text{O})-$.

228. The compound of any of claims 201-227 wherein R_2 is Cl.

229. The compound of any of claims 201-227 wherein R_2 is $-\text{CH}_2\text{CH}_3$.

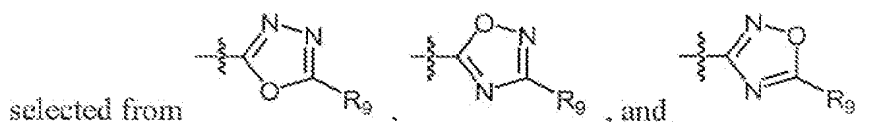
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230. The compound of any of claims 201-227 wherein R_2 is H.

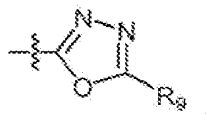
231. The compound of any of claims 201-227 wherein R_2 is $-\text{CH}_3$.

15 232. The compound of any of claims 201-227 wherein R_2 is other than H.

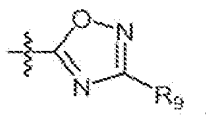
233. The compound of any of claims 201-209, 216, 219-223 and 225-232 wherein R_3 is



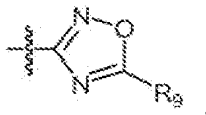
20 234. The compound of claim 233 wherein R_3 is



235. The compound of claim 233 wherein R_3 is



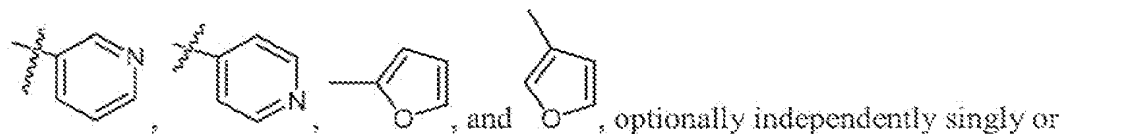
236. The compound of claim 233 wherein R_3 is



237. The compound of any of claims 201-209 wherein R_3 is $-OCH_3$.
238. The compound of any of the forgoing claims wherein R_4 is H.
- 5 239. The compound of any of claims 201-237 wherein R_4 is Cl.
240. The compound of any of the forgoing claims wherein R_5 is $-OCH_3$.
- 10 241. The compound of any of claims 201-239 wherein R_5 is $-CH_3$.
242. The compound of any of claims 201-239 wherein R_5 is H.
243. The compound of any of claims 201-239 wherein R_5 is F.
- 15 244. The compound of any of claims 201-239 wherein R_5 is Cl.
245. The compound of any of claims 201-244 wherein R_6 is H.
- 20 246. The compound of any of claims 201-244 wherein R_6 is Cl.
247. The compound of any of claims 201-244 wherein R_6 is F.
248. The compound of any of claims 201-247 wherein R_8 is F.
- 25 249. The compound of any of claims 201-247 wherein R_8 is Cl.
250. The compound of any of claims 201-247 wherein R_8 is Br.
- 30 251. The compound of any of claims 201-247 wherein R_8 is H.

252. The compound of any of claims 201-247 wherein R_8 is $-\text{OCH}_3$.

253. The compound of any of claims 201-252 wherein R_9 is selected from

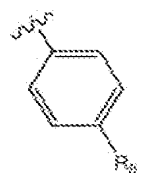


, optionally independently singly or multiply substituted.

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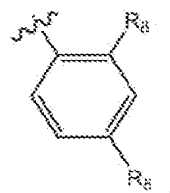
254. The compound of any of claims 201-253 wherein R_9 is not substituted.

255. The compound of any of claims 201 and 206-254 wherein R_7 is



10

256. The compound of any of claims 201 and 206-255 wherein R_7 is



257. The compound of any of claims 201-206, 210-226, 231-241, and 245-256 wherein n is 1, R_1 is $-\text{CH}_2-$, R_2 is $-\text{CH}_3$, R_3 is $-\text{CH}_3$ and R_5 is $-\text{CH}_3$.

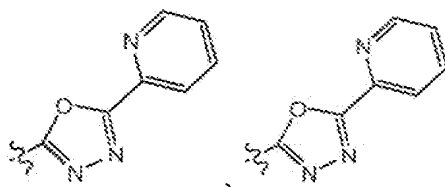
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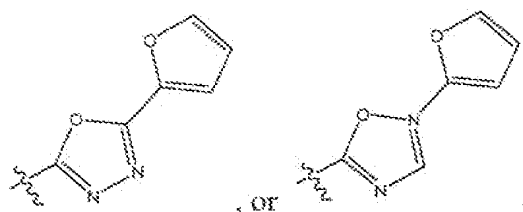
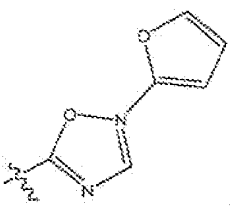
258. The compound of claim 201 or claim 202 wherein n is 0, R_1 is CH_2 , R_2 is $-\text{CH}_3$, R_5

is $-\text{OCH}_3$, R_6 is $-\text{H}$, and R_3 is , optionally independently singly or multiply substituted with R_9 .

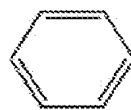
259. The compound of claim 201 or claim 202 wherein n is 0, R_1 is CH_2 , R_2 is $-\text{CH}_3$, R_5 is $-\text{OCH}_3$ and R_6 is $-\text{H}$.

260. The compound of claim 259 wherein R_3 is



5 , or , optionally independently substituted with one or more R_9 .

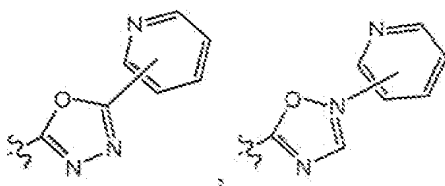
261. The compound of claim 259 or 260 wherein R_7 is

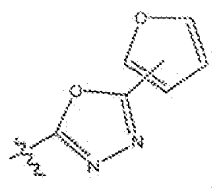
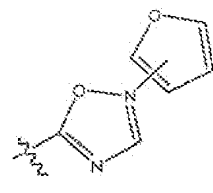


, optionally

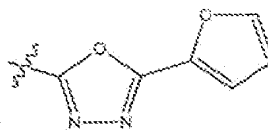
independently singly or multiply substituted with R_8 .

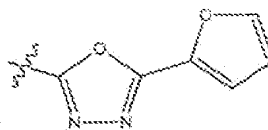
10 262. The compound of claim 259 wherein R_3 is



, or , optionally independently singly or multiply substituted with R_9 .

15 263. The compound of any of claims 259-262 wherein the one or more R_8 are independently selected from $-\text{OCH}_3$ and Cl .



264. The compound of claim 262 wherein R_3 is , optionally independently singly or multiply substituted with R_9 .

265. The compound of any of claims 201-264 having Formula I.

5

266. The compound of any of claims 201-264 having Formula II.

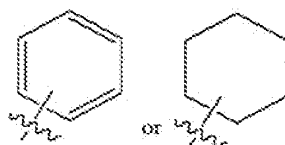
267. The compound of any of claims 201-215, 226-232, and 238-257 wherein R_{10} is



, optionally independently singly or multiply substituted with R_9 .

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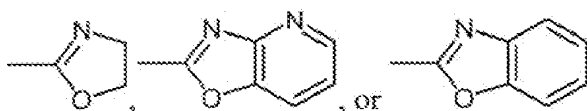
268. The compound of any of claims 201-215, 226-232, and 238-257 wherein R_{10} is



15

optionally independently substituted with one or more R_9 .

269. The compound of any of claims 201-215, 226-232, and 238-257 wherein R_{10} is



, optionally independently singly or multiply substituted with R_9 .

20

270. The compound of any of claims 201-215, 226-232, and 238-257 wherein R_3 is a monocyclic heteroaryl, wherein the heteroatoms are O or N.

25

271. The compound of any of claims 201-215, 226-232, and 238-257 wherein R_3 is a bicyclic heteroaryl, wherein the heteroatoms are O or N.

272. The compound of any claims 201-215, 226-232, and 238-257 wherein R_3 is a monocyclic heteroaryl having 5 ring atoms, wherein the heteroatoms are O or N.

5 273. The compound of any of claims 201-215, 226-232, and 238-257 wherein R_3 is a monocyclic heteroaryl having 6 ring atoms, wherein the heteroatoms are O or N.

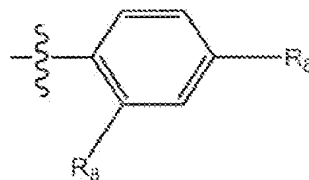
274. The compound of any of claims 201-273 wherein R_9 is a heteroaryl.

10 275. The compound of any of claims 201-273 wherein R_9 is C_6H_5 .

276. The compound of claim 261 wherein R_7 is

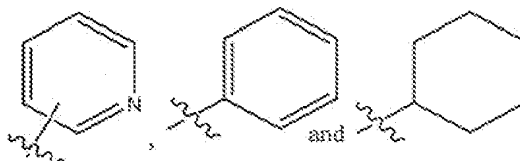


277. The compound of claim 261 wherein R_7 is



15

278. The compound of any of claims 201-209, 226-232 and 238-257 wherein n is 0, R_3

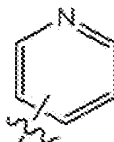


is $-C(O)NHR_{10}$ and R_{10} is selected from:

279. The compound of claim 276 or 277 wherein R_8 is Cl, Br, or $-OCH_3$.

20

280. The compound of any claims 201-236 wherein R_9 is a heteroaryl.



281. The compound of claim 280 wherein R₉ is

282. A pharmaceutical composition comprising a compound of any of claims 201-281 and a pharmaceutically acceptable carrier or excipient.

5

283. A method for preparing a pharmaceutical composition, the method comprising combining a compound of any of claims 201-281 and a pharmaceutically acceptable carrier or excipient.

10 284. A method for treating a patient comprising administering the compound of any of claims 201-281 or the pharmaceutical composition of claim 81.

285. A method for treating a patient for anxiety, comprising administering the compound of any of claims 201-281 or the pharmaceutical composition of claim 282.

15

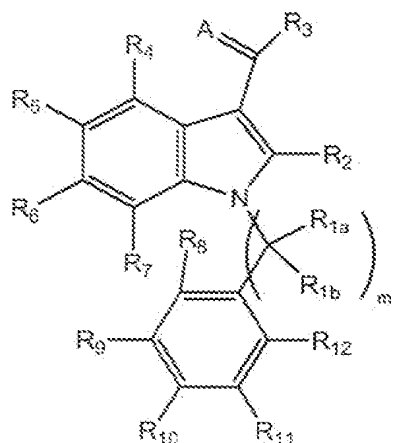
286. A method for treating a patient for depression, comprising administering the compound of any of claims 201-281 or the pharmaceutical composition of claim 282.

20 287. A method for treating a patient for pain, comprising administering the compound of any of claims 201-281 or the pharmaceutical composition of claim 282.

288. A method for treating a patient for obesity, comprising administering the compound of any of claims 201-281 or the pharmaceutical composition of claim 282.

25 289. A method for treating a patient for bipolar disorder, comprising administering the compound of any of claims 201-281 or the pharmaceutical composition of claim 282.

290. A compound having Formula I:



Formula I

Wherein:

A is O or NOCH₃;

- 5 each R_{1a} and R_{1b} is independently: H, halogen, hydroxyl, -CN, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, an optionally substituted C1-C5 alkoxy, -NO₂; or an R_{1a} and R_{1b} attached to the same carbon, taken together with that carbon, form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle; or an R_{1a} attached to a
- 10 carbon directly bonded to the ring bearing R₈, taken with R₈ and the carbon to which R_{1a} is attached, form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle; or an R_{1a} attached to a carbon directly bonded to the ring bearing R₁₂, taken with R₁₂ and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted
- 15 heterocycle;

m = 1, 2 or 3;

R₂ is H, hydroxyl, -NO₂, an optionally substituted C1-C5 alkoxy, -CN, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl or halogen;

R₃ is an optionally substituted heteroaryl;

- 5 each of R₄, R₅, R₆ and R₇ are independently: H, a halogen, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, hydroxyl, NO₂, an optionally substituted C1-C5 alkoxy, -CN, -C(O)OH, an optionally substituted -SO₂CH₃, an optionally substituted -SO₂NH₂, an optionally substituted -SO₂OH, -C(O)H, an optionally substituted -C(O)CH₃, an optionally substituted -C(O)N(CH₃)₂, an optionally substituted -C(O)NH₂, an optionally substituted -SCH₃, an optionally substituted heterocycle or heteroaromatic, or -N(R_{2a})(R_{2b});

15 wherein each R_{2a} and R_{2b} is independently: H, hydroxy, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl; an optionally substituted C2-C5 alkynyl; an optionally substituted C1-C5 alkoxy or an R_{2a} and R_{2b} attached to the same nitrogen, taken together with that nitrogen form an optionally substituted heterocycle or heteroaromatic;

and

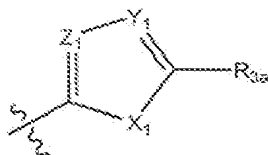
- each of R₈, R₉, R₁₀, R₁₁ and R₁₂ is independently H, -CN, hydroxyl, a halogen, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, hydroxyl, NO₂, an optionally substituted C1-C5 alkoxy, -N(R_{2a})(R_{2b}), -C(O)OH, an optionally substituted -SO₂CH₃, an optionally substituted -SO₂NH₂, an optionally substituted -SO₂OH, -C(O)H, an optionally substituted -C(O)CH₃, an optionally substituted -C(O)N(CH₃)₂, an optionally substituted -C(O)NH₂, an optionally substituted -SCH₃, an optionally substituted heterocycle or heteroaromatic, or
- 25 R₈ taken with an R_{1a} attached to a carbon directly bonded to the ring bearing R₈ and the carbon to which the R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle, or R₁₂ taken with an R_{1a} attached to a carbon directly bonded to the ring bearing R₁₂ and the carbon to which the R_{1a} is

attached, form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle

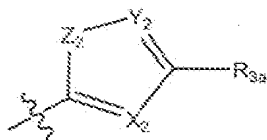
and pharmaceutically acceptable salts thereof.

291. The compound of claim 290 wherein

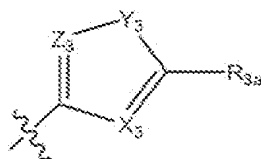
- 5 R_3 is selected from: R_{3x} , R_{3y} and R_{3z} wherein:



- R_{3x} is , wherein X_1 , Y_1 , and Z_1 are: (a) O, N and N, respectively; (b) O, N and C(R_{3c}), respectively; (c) O, C(R_{3c}) and C(R_{3c}), respectively; (d) O, C(R_{3c}) and N, respectively; (e) S, N and N, respectively; (f) S, N and C(R_{3c}), respectively; (g) S, C(R_{3c}) and C(R_{3c}), respectively; (h) S, C(R_{3c}) and N, respectively; (i) N(R_{3b}), N and N, respectively; (j) N(R_{3b}), N and C(R_{3c}), respectively; (k) N(R_{3b}), C(R_{3c}) and C(R_{3c}), respectively; or (l) N(R_{3b}), C(R_{3c}) and N, respectively;
- 10



- R_{3y} is , wherein X_2 , Y_2 , and Z_2 are: (a) N, N and O, respectively; (b) C(R_{3c}), N and O, respectively; (c) N, C(R_{3c}) and O, respectively; (d) C(R_{3c}), C(R_{3c}) and O, respectively; (e) N, N and S, respectively; (f) C(R_{3c}), N and S, respectively; (g) N, C(R_{3c}) and S, respectively; (h) C(R_{3c}), C(R_{3c}) and S, respectively; (i) N, N and N(R_{3b}), respectively; (j) C(R_{3c}), N and N(R_{3b}), respectively; (k) N, C(R_{3c}) and N(R_{3b}), respectively; or (l) C(R_{3c}), C(R_{3c}) and N(R_{3b}), respectively;
- 15



- R_{3a} is _____, wherein X_3 , Y_3 , and Z_3 are: (a) N, O and N, respectively; (b) $C(R_{3c})$, O and N, respectively; (c) N, O and $C(R_{3c})$, respectively; (d) $C(R_{3c})$, O and C, respectively; (e) N, S and N, respectively; (f) $C(R_{3c})$, S and N, respectively; (g) N, S and C, respectively; (h) $C(R_{3c})$, S and $C(R_{3c})$, respectively; (i) N, $N(R_{3b})$ and N, respectively; 5 (j) $C(R_{3c})$, $N(R_{3b})$ and N, respectively; (k) N, $N(R_{3b})$ and $C(R_{3c})$, respectively; or (l) $C(R_{3c})$, $N(R_{3b})$ and $C(R_{3c})$, respectively;

R_{3a} is selected from:

- H, halogen, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, an optionally substituted C1-C5 alkoxy, $-NO_2$, $-CN$, $-C(O)OH$, an optionally substituted $-SO_2CH_3$, an optionally substituted $-SO_2NH_2$, an optionally substituted $-SO_2OH$, $-C(O)H$, an optionally substituted $-C(O)CH_3$, an optionally substituted $-C(O)N(CH_3)_2$, an optionally substituted $-C(O)NH_2$, an optionally substituted $-SCH_3$, an optionally substituted C3 to C10 cycloalkyl or carbocycle, an optionally substituted heterocycle, or R_{3a} and the carbon to which it is attached together with Y_1 , Y_2 or Y_3 can form a heteroaryl containing 5 to 6 ring atoms or R_{3a} is absent. 15

R_{3b} is selected from:

- H, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, an optionally substituted C1-C5 alkoxy, $-CN$, an optionally substituted $-SO_2CH_3$, an optionally substituted $-SO_2NH_2$, an optionally substituted $-SO_2OH$, an optionally substituted $-C(O)CH_3$, an optionally substituted $-C(O)N(CH_3)_2$, an optionally substituted $-C(O)NH_2$, an optionally substituted C3 to C10 cycloalkyl or carbocycle, an optionally substituted heterocycle; 20

R_{3c} is selected from:

H, halogen, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, an optionally substituted C1-C5 alkoxy, -NO₂, -CN, -C(O)OH, an optionally substituted -SO₂CH₃, an optionally substituted -SO₂NH₂, an optionally substituted -SO₂OH, -C(O)H, an optionally substituted -C(O)CH₃, an optionally substituted -C(O)N(CH₃)₂, an optionally substituted -C(O)NH₂, an optionally substituted -SCH₃, an optionally substituted C3 to C10 cycloalkyl or carbocycle, an optionally substituted heterocycle, or R_{3c} and the carbon to which it is attached together with a ring atom bonded to the carbon to which R_{3c} is attached can form a heteroaryl containing 5 to 6 ring atoms.

292. The compound of claim 290 or claim 291 wherein R₂ is selected from H, methyl, Cl and CF₃ and F.

293. The compound of any of the forgoing claims wherein R₂ is selected from H, methyl and Cl.

294. The compound of claim 290 or claim 291 wherein R₂ is halogen.

295. The compound of claim 290 or claim 291 wherein R₂ is Cl.

296. The compound of claim 290 or claim 291 wherein R₂ is F.

297. The compound of any of claims 290-296 wherein R₂ is methyl.

298. The compound of any of claims 290-297 wherein R₂ is methyl or halogen substituted methyl.

299. The compound of any of claims 290-298 wherein m is one.

300. The compound of any of claims 290-299 wherein R_{1a} and R_{1b} taken together with the carbon to which they are attached form an optionally substituted C3-C6 cycloalkyl or carbocycle.

301. The compound of any of claims 290-299 wherein R_{1a} and R_{1b} are both H.

5 302. The compound of any of claims 290-299 wherein R_{1a} and R_{1b} are either both methyl or taken together with the carbon to which they are attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle.

303. The compound of any of claims 290-299 wherein the R_{1a} attached to a carbon directly bonded to the ring bearing R_{12} , taken with R_{12} and the carbon to which R_{1a} is
10 attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle or the R_{1a} attached to a carbon directly bonded to the ring bearing R_8 , taken with R_8 and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle.

304. The compound of any of claims 290-299 wherein m is 1 and R_{1a} and R_{1b} taken
15 together with the carbon to which they are attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle.

305. The compound of any of claims 290-299 wherein R_{1a} and R_{1b} attached to the same carbon, taken together with that carbon, form an optionally substituted C3-C6 cycloalkyl or carbocycle.

20 306. The compound of any of claims 290-305 wherein R_9 and R_{11} are both H.

307. The compound of any of claims 290-206 wherein no more than four of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.

308. The compound of any of claims 290-307 wherein no more than three of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.

309. The compound of any of claims 290-308 wherein no more than two of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.

310. The compound of any of claims 290-309 wherein only one of R_8 , R_9 , R_{10} , R_{11} and R_{12} is other than H.

5 311. The compound of any of claims 290-310 wherein R_5 is methoxy.

312. The compound of any of claims 290-311 wherein R_{10} is halogen.

313. The compound of any of claims 290-312 wherein R_4 is selected from: F, H, an optionally substituted C1-C5 alkyl, an optionally substituted C1-C5 alkoxy.

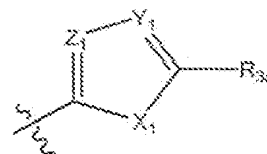
10 314. The compound of any of claims 290-313 wherein each of R_4 , R_5 , R_6 , and R_7 is independently selected from H, a halogen, hydroxy, an optionally substituted C1-C5 alkyl, an optionally substituted C1-C5 alkoxy.

315. The compound of any of claims 290-314 wherein R_5 is selected from: Cl, F, Br, methoxy, CH_3 , CF_3 and OH.

316. The compound of any of claims 291-315 wherein R_3 is R_{3x} .

15 317. The compound of any of claims 291-315 wherein R_3 is R_{3y} .

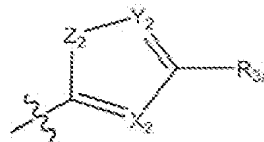
318. The compound of any of claims 291-315 wherein R_3 is R_{3z} .



319. The compound of any of claims 290-315 wherein R_{3x} is
 wherein X_1 , Y_1 , and Z_1 are: (a) O, N and N, respectively; (b) O, N and $C(R_{3c})$,
 20 respectively; (c) O, $C(R_{3c})$ and $C(R_{3c})$, respectively; (d) O, $C(R_{3c})$ and N respectively; (e)

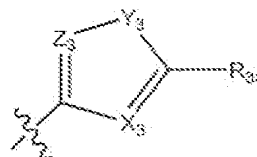
S, N and N, respectively; (f) S, N and C(R_{3c}), respectively; (g) S, C(R_{3c}) and C(R_{3c}), respectively; (h) S, C(R_{3c}) and N respectively; (i) N(R_{3b}), N and N, respectively; (j) N(R_{3b}), N and C(R_{3c}), respectively; (k) N(R_{3b}), C(R_{3c}) and C(R_{3c}), respectively; or (l) N(R_{3b}), C(R_{3c}) and N respectively.

- 5 320. The compound of claim 319 wherein R₃ is R_{3x} and X₁, Y₁, and Z₁ are (k) O, N and N, respectively.

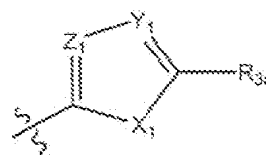


321. The compound of any of claims 290-315 wherein R_{3y} is
 wherein X₂, Y₂, and Z₂ are: (a) N, N and O, respectively; (b) C(R_{3c}), N and O,
 respectively; (c) N, C(R_{3c}) and O, respectively; (d) C(R_{3c}), C(R_{3c}) and O, respectively; (e)
 10 N, N and S, respectively; (f) C(R_{3c}), N and S, respectively; (g) N, C(R_{3c}) and S,
 respectively; (h) C(R_{3c}), C(R_{3c}) and S, respectively; (i) N, N and N(R_{3b}), respectively; (j)
 C(R_{3c}), N and N(R_{3b}), respectively; (k) N, C(R_{3c}) and N(R_{3b}), respectively; or (l) C(R_{3c}),
 C(R_{3c}) and N(R_{3b}), respectively.

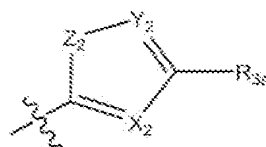
322. The compound of claim 321 wherein R₃ is R_{3y} and X₂, Y₂, and Z₂ are (e) N, N and
 15 O, respectively.



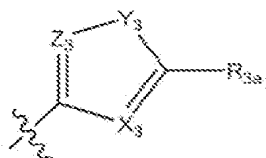
323. The compound of any of claims 290-315 wherein R_{3z} is
 wherein X₃, Y₃, and Z₃ are: (a) N, O and N, respectively; (b) C(R_{3c}), O and N,
 respectively; (c) N, O and C(R_{3c}), respectively; (d) C(R_{3c}), O and C, respectively; (e) N, S
 and N, respectively; (f) C(R_{3c}), S and N, respectively; (g) N, S and C, respectively; (h)
 20 C(R_{3c}), S and C(R_{3c}), respectively; (i) N, N(R_{3b}) and N, respectively; (j) C(R_{3c}), N(R_{3b})
 and N, respectively; (k) N, N(R_{3b}) and C(R_{3c}), respectively; or (l) C(R_{3c}), N(R_{3b}) and
 C(R_{3c}), respectively.



324. The compound of any of claims 290-315 wherein R_{3x} is wherein X_1 , Y_1 , and Z_1 are: (i) O, N and $C(R_{3c})$, respectively; (j) O, $C(R_{3c})$ and N, respectively; or (k) O, N and N respectively.



5 325. The compound of any of claims 290-315 wherein R_{3y} is wherein X, Y, and Z are: (c) N, N and O, respectively.



326. The compound of any of claims 290-315 wherein R_{3z} is wherein X, Y, and Z are: (a) $C(R_{3c})$, O and N, respectively, (b) $C(R_{3c})$, S and N, respectively; (c) N, O and N, respectively; (d) N, S and N, respectively; or (e) N, $N(R_{3b})$ and N, respectively; and

R_{3a} is an optionally substituted aryl containing a single ring or an optionally substituted heteroaryl containing a single ring.

327. The compound of any of claims 290-326 wherein R_4 is H.

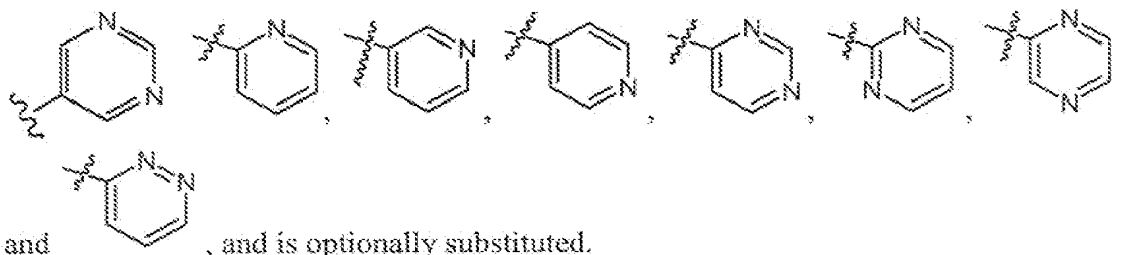
328. The compound of any of claims 290-327 wherein R_6 is H.

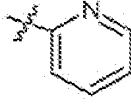
15 329. The compound of any of claims 290-328 wherein R_7 is H.

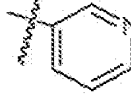
330. The compound of any of claims 290-329 wherein R_8 is H.

331. The compound of any of claims 290-330 wherein R_4 , R_5 , and R_7 are H.

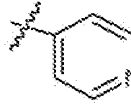
332. The compound of any of claims 290-331 wherein R_{3a} is selected from:

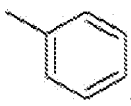


333. The compound of claim 332 wherein R_{3a} is  and is optionally substituted.

334. The compound of claim 332 wherein R_{3a} is  and is optionally substituted.

10

335. The compound of claim 332 wherein R_{3a} is  and is optionally substituted.

336. The compound of claim 332 wherein R_{3a} is  and is optionally substituted.

337. The compound of any of claims 291-331 wherein R_{3a} is an optionally substituted pyrimidine.

15

338. The compound of any of claims 291-337 wherein R_{3a} is monosubstituted or unsubstituted.

339. The compound of any of claims 291-338 wherein R_{3a} is unsubstituted.

343. The compound of any of claims 290-342 wherein R_{3c} is selected from H, halogen and C1-C3 alkyl.

344. The compound of any of claims 290-343 wherein R_{3c} taken with the carbon to which it is attached and a ring atom adjacent to the ring atom to which it is attached form a heteroaryl.

345. The compound of any of claims 290-344 wherein an R_{1a} attached to a carbon directly bonded to the ring bearing R_8 , taken with R_8 and the carbon to which R_{1a} is attached, form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle; or an R_{1b} attached to a carbon directly bonded to the ring bearing R_{12} , taken with R_{12} and the carbon to which R_{1b} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle and R_{1b} is selected from H or methyl.

346. The compound of any of claims 290-345 wherein R_4 is an optionally substituted heterocycle or heteroaromatic containing 5 or 6 ring atoms.

347. The compound of any of claims 290-346 wherein R_5 is an optionally substituted heterocycle or heteroaromatic containing 5 or 6 ring atoms.

348. The compound of any of claims 290-347 wherein R_6 is an optionally substituted heterocycle or heteroaromatic containing 5 or 6 ring atoms.

349. The compound of any of claims 290-348 wherein R_7 is an optionally substituted heterocycle or heteroaromatic containing 5 or 6 ring atoms.

350. The compound of any of claims 290-349 wherein, R_{2a} and R_{2b} attached to the same nitrogen, taken together with that nitrogen form an optionally substituted heterocycle or heteroaromatic containing 5 or 6 ring atoms.

351. The compound of any of claims 290-350 wherein R₈ heterocycle or heteroaromatic containing 5 or 6 ring atoms.

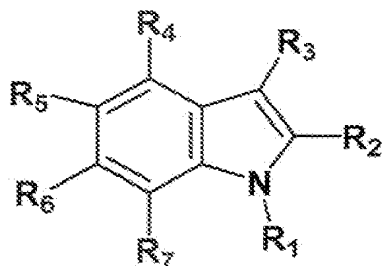
352. The compound of any of claims 290-351 wherein R₉ heterocycle or
5 heteroaromatic containing 5 or 6 ring atoms.

353. The compound of any of claims 290-352 wherein R₁₀ heterocycle or heteroaromatic containing 5 or 6 ring atoms.

354. The compound of any of claims 290-353 wherein R₁₁ heterocycle or heteroaromatic containing 5 or 6 ring atoms.

10 355. The compound of any of claims 290-354 wherein R₁₂ heterocycle or heteroaromatic containing 5 or 6 ring atoms.

356. A compound having Formula II:



15 Formula II

wherein R₂, R₃, R₄, and R₇ are independently selected from: H, CO₂H, halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle-C(O)R₈, -(CH₂)_nC(O)NO, -(CH₂)_nN(H)-aryl, -C(O)N(H)-aryl, -OR₈, -C(O)N(OH)(C1-C6 alkyl), -C(O)N(H)(NH₂), -NR₈, -N(H)OR₈, -(CH₂)_nC(O)OR₈, -S(CH₂)_nCO₂H, -N(CH₂)_nCO₂H, -

ON(H)(CH₂)_nCO₂H, -SO₃H, -PO₃H₂ -(CH₂)_naryl, -(CH₂)_nNH₂, -(CH₂)_nN(OH)(C₁-C₆
 aryl), -NO₂, -SR₈, -SOR₈, -SO₂R₈, -(CH₂)_nCN, -(CH₂)_nO-carbocycle, -(CH₂)_nS-
 carbocycle, -(CH₂)_nS-cycloalkyl, -(CH₂)_nS(O)₂-carbocycle, -(CH₂)_nS(O)₂-carbocycle, -
 (CH₂)_nN(H)carbocycle, (CH₂)_nNCOCH₃, -(CH₂)_n-carbocycle, -O(CH₂)_nCO₂H, CN₃H,
 5 (CH₂)_nCN₃H, -B(OH)₂, -(CH₂)_nN(OH),

R₅ is selected from H, halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl,
 heteroaryl, heterocycle, carbocycle -C(O)R₈, CO₂H, -NR₈, -NOR₈, -NO₂, -SR₈, -SOR₈, -
 SO₂R₈;

R₆ is selected from: H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl,
 10 heterocycle, carbocycle, OH, -OR₈, -NR₈, -NOR₈, -NO₂, -SR₈, -SOR₈, -SO₂R₈;

R₁ is selected from: H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl,
 heterocycle, carbocycle, (CH₂)_ncarbocycle, (CH₂)_nphenyl.

wherein R₈ is selected from H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl,
 heteroaryl, heterocycle, carbocycle;

15 n = 0, 1, 2, 3, 4 or 5; and

any C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle
 can be optionally substituted and pharmaceutically acceptable salts thereof.

357. The compound of claim 357 wherein:

R₂, R₃, R₄, and R₇ are independently selected from: H, CO₂H, halogen, C1-C6 alkyl, C2-
 20 C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle -C(O)R₈, -
 (CH₂)_nC(O)NO, -(CH₂)_nN(H)-aryl, -C(O)N(H)-aryl, -OR₈, -C(O)N(OH)(C1-C6 alkyl), -
 C(O)N(H)(NH₂), -NR₈, -N(H)OR₈, -(CH₂)_nC(O)OR₈, -S(CH₂)_nCO₂H, -N(CH₂)_nCO₂H, -
 ON(H)(CH₂)_nCO₂H, -SO₃H, -PO₃H₂ -(CH₂)_naryl, -(CH₂)_nNH₂, -(CH₂)_nN(OH)(C₁-C₆
 aryl), -NO₂, -SR₈, -SOR₈, -SO₂R₈, -(CH₂)_nCN, -(CH₂)_nO-carbocycle, -(CH₂)_nS-
 25 carbocycle, -(CH₂)_nS-cycloalkyl, -(CH₂)_nS(O)₂-carbocycle, -(CH₂)_nS(O)₂-carbocycle, -
 (CH₂)_nN(H)carbocycle, and (CH₂)_nNCOCH₃.

358. The compound of claim 357 wherein:

R₂, R₃, R₄, and R₇ are independently selected from: H, CO₂H, halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle -C(O)R₈, -
 (CH₂)_nC(O)NO, -(CH₂)_nN(H)-aryl, -C(O)N(H)-aryl, -OR₈, -C(O)N(OH)(C1-C6 alkyl), -
 5 C(O)N(H)(NH₂), -NR₈, -N(H)OR₈, -(CH₂)_nC(O)OR₈.

359. The compound of claim 356 wherein:

R₂, R₃, R₄, and R₇ are independently selected from: H, CO₂H, halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle -C(O)R₈, -
 (CH₂)_nC(O)NO, -(CH₂)_nN(H)-aryl, -C(O)N(H)-aryl, -OR₈.

10 360. The compound of any of claims 356-359 wherein:

R₅ is selected from H, halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle -C(O)R₈, -NR₈, -NOR₈, -NO₂, -SR₈, -SOR₈, -SO₂R₈.

361. The compound of any of claims 356-360 wherein:

15 R₅ is selected from H, halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle -C(O)R₈.

362. The compound of any of claims 356-361 wherein:

R₆ is selected from: H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle, OH, -OR₈, -NR₈, -NOR₈, -NO₂, -SR₈, -SOR₈, -SO₂R₈.

363. The compound of any of claims 356-362 wherein:

20 R₆ is H.

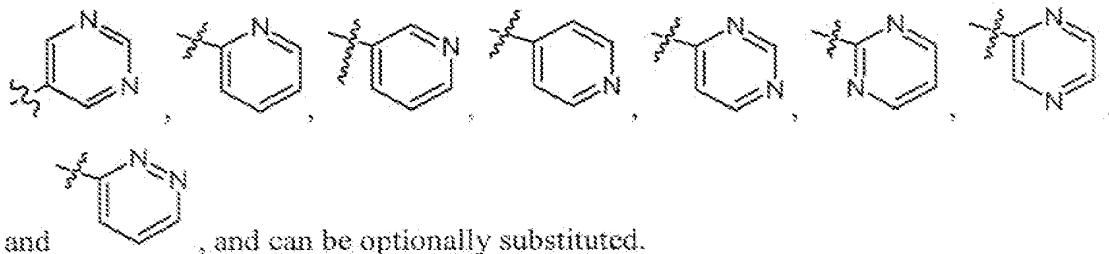
364. The compound of any of claims 356-363 wherein:

R₁ is selected from: H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle, (CH₂)_ncarbocycle.

365. The compound of any of claims 356-364 wherein:

R₁ is H.

5 366. The compound of any of claims 356-365 wherein any heteroaryl is selected from:



10 367. The compound of any of claims 356-365 wherein the any aryl or carbocycle is a phenyl.

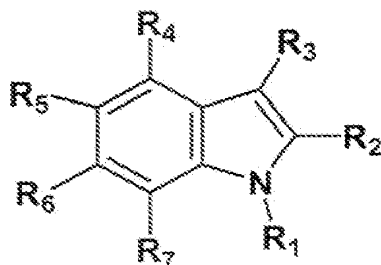
368. The compound of any of claims 356-365 wherein any heteroaryl contains 5 or 6 ring atoms.

369. The compound of any of claims 356-365 wherein any heterocycle contains 5 or 6 ring atoms.

15 370. The compound of any of claims 356-369 wherein any C1-C6 alkyl is methyl or ethyl.

371. The compound of any of claim 356-370 wherein R₁ is (CH₂)phenyl.

372. A compound having Formula III:



Formula III

wherein R_2 , R_3 , R_4 , and R_5 are independently selected from: H, $-OR_8$, CO_2H , halogen,
 5 C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle -
 $C(O)R_8$, $-(CH_2)_n C(O)NO$, $-(CH_2)_n N(H)aryl$, $-C(O)N(H)aryl$, $-C(O)N(OH)(C1-C6 \text{ alkyl})$, $-$
 $C(O)N(H)(NH_2)$, $-NR_8$, $-N(H)OR_8$, $-(CH_2)_n C(O)OR_8$, $-S(CH_2)_n CO_2H$, $-N(CH_2)_n CO_2H$, $-$
 $ON(H)(CH_2)_n CO_2H$, $-SO_3H$, $-PO_3H_2$, $-(CH_2)_n aryl$, $-(CH_2)_n NH_2$, $-(CH_2)_n N(OH)(C1-C6$
 aryl), $-NO_2$, $-SR_8$, $-SOR_8$, $-SO_2R_8$, $-(CH_2)_n CN$, $-(CH_2)_n Ocarbocycle$, $-(CH_2)_n Scarbocycle$,
 10 $-(CH_2)_n Scycloalkyl$, $-(CH_2)_n S(O)_2 carbocycle$, $-(CH_2)_n S(O)_2 carbocycle$, $-$
 $(CH_2)_n N(H)carbocycle$, $(CH_2)_n NCOCH_3$, $-(CH_2)_n carbocycle$, $-O(CH_2)_n CO_2H$, CN_5H ,
 $(CH_2)_n CN_5H$, $B(OH)_2$, $(CH_2)_n N(OH)$,

R_6 is selected from H, halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl,
 heteroaryl, heterocycle, carbocycle $-C(O)R_8$, CO_2H , $-NR_8$, $-NOR_8$, $-NO_2$, $-SR_8$, $-SOR_8$, $-$
 15 SO_2R_8 ;

R_7 is H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle,
 carbocycle, OH, $-OR_8$, $-NR_8$, $-NOR_8$, $-NO_2$, $-SR_8$, $-SOR_8$, $-SO_2R_8$;

R_1 is H;

$n = 0, 1, 2, 3, 4$ or 5 ; and

20 wherein R_8 is H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl,
 heterocycle, carbocycle; and

and wherein any C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle can be optionally substituted and pharmaceutically acceptable salts thereof.

373. The compound of claim 372 wherein:

- 5 R_2 , R_3 , R_4 , R_5 , and R_8 are independently selected from: H, and -OR₈, CO₂H, halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl.

374. The compound of claim 372 wherein:

R_2 , R_3 , R_4 , R_5 , and R_8 are independently selected from: H, and -OR₈.

375. The compound of any of claims 372-374 wherein R_6 is selected from H, halogen,
10 C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl,

376. The compound of any of claims 372-374 wherein R_6 is H.

377. The compound of any of claims 372-374 wherein:

R_7 is H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, heteroaryl, heterocycle, carbocycle, OH, -OR₈, -NR₈, -NOR₈, -NO₂, -SR₈, -SOR₈, -SO₂R₈.

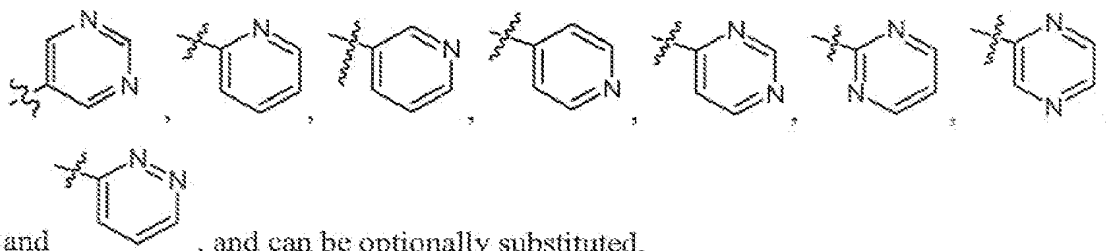
- 15 378. The compound of any of claims 372-374 wherein:

R_7 is H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl.

379. The compound of any of claims 372-378 wherein:

R_7 is H.

380. The compound of any of claims 372-379 wherein any heteroaryl is selected from:



381. The compound of any of claims 372-380 wherein the any aryl is a phenyl.

5 382. The compound of any of claims 372-380 wherein any heteroaryl contains 5 or 6 ring atoms.

383. The compound of any of claims 372-380 wherein any heterocycle contains 5 or 6 ring atoms.

10 384. The compound of any of claims 372-380 wherein any C1-C6 alkyl is methyl or ethyl.

385. A pharmaceutical composition comprising a compound of any of claims 290-384 and a pharmaceutically acceptable carrier or excipient.

15 386. A method for preparing a pharmaceutical composition, the method comprising combining a compound of any of claims 290-384 and a pharmaceutically acceptable carrier or excipient.

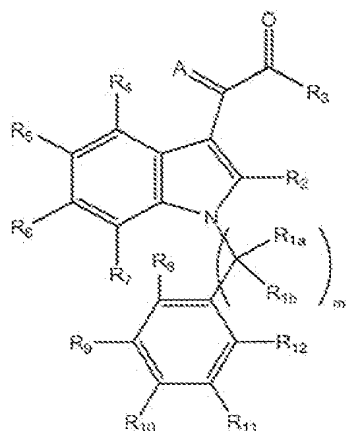
387. A method for treating a patient comprising administering the compound of any of claims 290-384 or the pharmaceutical composition of claim 385.

388. A method for treating a patient for an FAAH-related disorder, comprising administering the compound of any of claims 290-355.

20 389. The method of claim 388 wherein the disorder is anxiety or anxiety.

390. A method for treating a patient for a DAO-related disorder, comprising administering the compound of any of claims 356-384.

391. A compound having the formula:



wherein

A is O or NOCH₃;

- 5 each R_{1a} and R_{1b} is independently: H, halogen, hydroxyl, -CN, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, an optionally substituted C1-C5 alkoxy, -NO₂; or an R_{1a} and R_{1b} attached to the same carbon, taken together with that carbon, form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle; or an R_{1a} attached to a carbon directly bonded to the ring bearing R₈, taken with R₈ and the carbon to which R_{1a} is attached, form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle; or an R_{1a} attached to a carbon directly bonded to the ring bearing R₁₂, taken with R₁₂ and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle;
- 10
- 15

m = 1, 2 or 3;

R₂ is H, hydroxyl, -NO₂, an optionally substituted C1-C5 alkoxy, -CN, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl or halogen;

R₃ is H, OH, optionally substituted C1-C10 alkyl, optionally substituted C2-C10 alkenyl, an optionally substituted C2-C10 alkynyl, optionally substituted C1-C10 alkoxy, -OR_{3a}, -OR_{3b}, -SR_{3a}, -SR_{3b}, -N(R_{3a})(R_{3b}), -N(R_{3a})(R_{3a}), -N(R_{3b})(R_{3b}), an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an
5 optionally substituted carbocycle or an optionally substituted heterocycle;

R_{3a} is H or an optionally substituted C1 to C10 alkyl an optionally substituted C2-C10 alkenyl, an optionally substituted C2-C10 alkynyl or R_{3a} and R_{3b} taken together with the N to which they are attached can form a heterocycle or heteroaryl;

R_{3b} is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally
10 substituted cycloalkyl, an optionally substituted carbocycle, an optionally substituted heterocycle, or an optionally substituted C1 to C10 alkyl, an optionally substituted C2-C10 alkenyl, an optionally substituted C2-C10 alkynyl or R_{3a} and R_{3b} taken together with the N to which they are attached can form a heterocycle or heteroaryl;

each of R₄, R₅, R₆ and R₇ are independently: H, a halogen, an optionally substituted C1-
15 C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, hydroxyl, NO₂, an optionally substituted C1-C5 alkoxy, -CN, -C(O)OH, an optionally substituted -SO₂CH₃, an optionally substituted -SO₂NH₂, an optionally substituted -SO₂OH, -C(O)H, an optionally substituted -C(O)CH₃, an optionally substituted -C(O)N(CH₃)₂, an optionally substituted -C(O)NH₂, an optionally substituted
20 -SCH₃, an optionally substituted heterocycle or heteroaromatic, or -N(R_{2a})(R_{2b});

wherein each R_{2a} and R_{2b} is independently: H, hydroxy, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl; an optionally substituted C2-C5 alkynyl; an optionally substituted C1-C5 alkoxy or an R_{2a} and R_{2b} attached to the same nitrogen, taken together with that nitrogen form an optionally substituted heterocycle or
25 heteroaromatic;

and

- each of R_8 , R_9 , R_{10} , R_{11} and R_{12} is independently H, -CN, hydroxyl, a halogen, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, hydroxyl, NO_2 , an optionally substituted C1-C5 alkoxy, - $\text{N}(\text{R}_{2a})(\text{R}_{2b})$, - $\text{C}(\text{O})\text{OH}$, an optionally substituted - SO_2CH_3 , an optionally substituted - SO_2NH_2 , an optionally substituted - SO_2OH , - $\text{C}(\text{O})\text{H}$, an optionally substituted - $\text{C}(\text{O})\text{CH}_3$, an optionally substituted - $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, an optionally substituted - $\text{C}(\text{O})\text{NH}_2$, an optionally substituted - SCH_3 , an optionally substituted heterocycle or heteroaromatic, or an R_{1a} attached to a carbon directly bonded to the ring bearing R_8 , taken with R_8 and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle, or an R_{1a} attached to a carbon directly bonded to the ring bearing R_{12} , taken with R_{12} and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle.
- 5
- 10

392. The compound of claim 391 wherein R_2 is H

- 15 393. The compound of claim 391 wherein R_2 is an optionally substituted C1-C5 alkyl or halogen.

394. The compound of claim 391 wherein R_2 is an optionally substituted methyl.

395. The compound of claim 391 wherein R_2 is halogen.

396. The compound of claim 391 wherein R_2 is F.

- 20 397. The compound of claim 391 wherein R_2 is Cl.

398. The compound of claim 391 wherein R_2 is an optionally substituted C1-C5 alkyl.

399. The compound of claim 391 wherein R_2 is methyl.

400. The compound of claim 391 wherein R_2 is selected from optionally substituted C1-C3 alkyl, Cl, and CF_3 .
401. The compound of claim 391 wherein R_2 is methyl or ethyl.
402. The compound of claim 391 wherein R_2 is Cl or singly or multiply fluorinated
5 methyl or ethyl.
403. The compound of claims 391- 402 wherein m is one.
404. The compound of any of claims 391-402 wherein R_{1a} and R_{1b} are both H.
405. The compound of any of claims 391-403 wherein R_{1a} and R_{1b} are both methyl.
406. The compound of any of claims 391-403 wherein the R_{1a} attached to a carbon
10 directly bonded to the ring bearing R_8 , taken with R_8 and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl.
407. The compound of any of claims 391-403 wherein the attached to a carbon directly bonded to the ring bearing R_{12} , taken with R_{12} and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl.
- 15 408. The compound of any of claims 391-402 wherein m is 1 and R_{1a} and R_{1b} taken together with the carbon to which they are attached form an optionally substituted C3-C6 cycloalkyl.
409. The compound of any of claims 391-403 wherein R_{1a} and R_{1b} attached to the same carbon, taken together with that carbon, form an optionally substituted heterocycle.
- 20 410. The compound of any of claims 391-409 wherein R_9 and R_{11} are both H.
411. The compound of any of claims 391-410 wherein R_4 is H.

412. The compound of any of claims 391-411 wherein each of R_4 , R_5 , R_6 , and R_7 is independently selected from H, a halogen, an optionally substituted C1-C5 alkyl, hydroxyl, and an optionally substituted C1-C5 alkoxy.

5 413. The compound of any of claims 391-412 wherein no more than four of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.

414. The compound of any of claims 391-413 wherein no more than three of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.

415. The compound of any of claims 391-414 wherein no more than two of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.

10 416. The compound of any of claims 391-415 wherein only one of R_8 , R_9 , R_{10} , R_{11} and R_{12} is other than H.

417. The compound of any of claims 391-414 wherein R_{3a} is H.

418. The compound of any of claims 391-416 wherein R_{3a} is methyl or ethyl.

15 419. The compound of any of claims 391-416 wherein R_{3b} is an optionally substituted aryl containing a single ring or an optionally substituted heteroaryl containing a single ring.

420. The compound of any of claims 391-416 wherein R_{3b} is an optionally substituted C6 aryl.

20 421. The compound of any of claims 391-416 wherein R_{3b} is an optionally substituted heteroaryl ring containing 6 ring atoms.

422. The compound of any of claims 391-416 wherein R_{3b} is an optionally substituted heteroaryl ring containing 5 ring atoms.

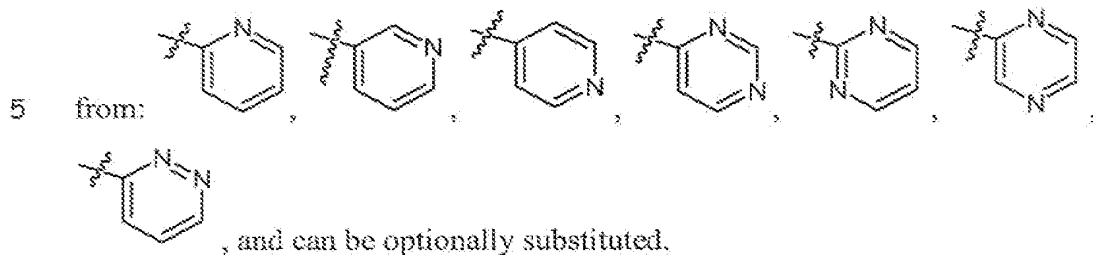
423. The compound of any of claims 391-416 wherein R_3 an optionally substituted heteroaryl.

424. The compound of any of claims 391-416 wherein R_3 is an optionally substituted morpholino.
425. The compound of any of claims 391-416 wherein R_3 is an optionally substituted aryl.
- 5 426. The compound of any of claims 391-416 wherein R_3 is an optionally substituted C3-C6 cycloalkyl.
427. The compound of any of claims 391-416 wherein R_{3b} is a 6, 5-fused heteroaryl.
428. The compound of any of claims 391-416 wherein R_{3b} is a heteroaryl containing 6 ring atoms of which up to two are N.
- 10 429. The compound of any of claims 391-416 where R_3 is $-N(R_{3a})(R_{3b})$, R_{3a} is H and R_{3b} is six-membered heteroaryl containing one or two N.
430. The compound of any claims 391-429 wherein any optional substitution is independently selected from: halogen, hydroxy, CN, C1-C3 alkyl, halogen substituted C1-C3 alkyl, C1-C3 alkoxy, and halogen substituted C1-C3 alkoxy.
- 15 431. The compound of any of claims 391-430 wherein R_{10} is Cl, an optionally halogen substituted methyl or an optionally halogen substituted methoxy.
432. The compound of any of claims 391-431 wherein R_7 is H.
433. The compound of any claims 391-416 wherein R_3 is $-N(H)R_{3b}$.
434. The compound of any of claims 391-433 wherein R_5 is an optionally halogen substituted methyl or an optionally halogen substituted methoxy.
- 20 435. The compound of any of claims 391-434 wherein at least one of R_4 , R_6 , and R_7 is H.

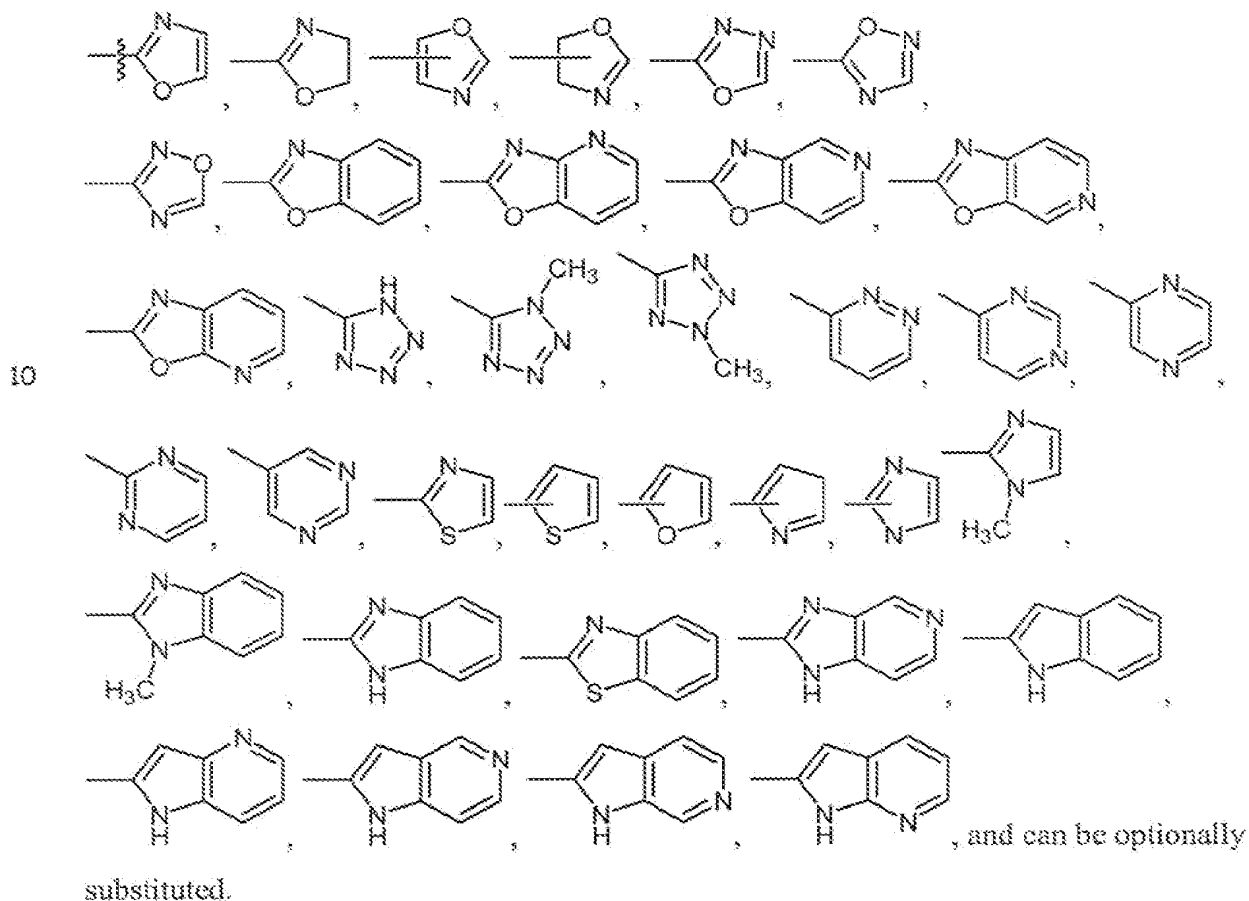
436. The compound of any of claims 391-435 wherein at least two of R_4 , R_6 , and R_7 are H.

437. The compound of any of the claims 391-436 wherein R_4 , R_6 , and R_7 are H.

438. The compound of claim 391 wherein R_{3b} is selected from:



439. The compound of claim 391 wherein R_{3b} is selected from:



440. The compound of any of claims 391-416 wherein R_{3b} is selected from an optionally substituted pyridinyl group, an optionally substituted pyrimidinyl group and an optionally substituted phenyl group.

5 441. The compound of any of claims 391-416 wherein R_{3b} is an optionally substituted pyridinyl group.

442. The compound of any of claims 391-416 wherein R_{3b} is an optionally substituted pyrimidinyl group.

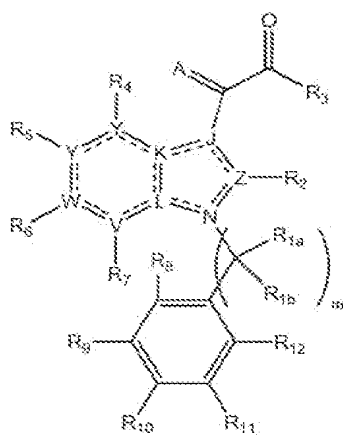
443. The compound of any of claims 391-416 wherein R_{3b} is an optionally substituted
10 phenyl group.

444. The compound of any of claims 391-443 wherein A is O.

445. The compound of any of claims 391-444 wherein A is NOCH_3 .

446. A compound of any of claims 391-445 wherein R_3 is $-\text{N}(\text{R}_{3a})(\text{R}_{3b})$.


15 447. A compound having the formula:



Wherein:

V, W, X, Y and Z are independently N or C

A is O or NOCH₃;

5  indicates a double or single bond;

each R_{1a} and R_{1b} is independently: H, halogen, hydroxyl, -CN, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, an optionally substituted C1-C5 alkoxy, -NO₂; or an R_{1a} and R_{1b} attached to the same carbon, taken together with that carbon, form an optionally substituted C3-C6
10 cycloalkyl or carbocycle or an optionally substituted heterocycle; or an R_{1a} attached to a carbon directly bonded to the ring bearing R₈, taken with R₈ and the carbon to which R_{1a} is attached, form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle; or an R_{1a} attached to a carbon directly bonded to the ring bearing R₁₂, taken with R₁₂ and the carbon to which R_{1a} is attached form an
15 optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle;

m = 1, 2 or 3;

R₂ is H, hydroxyl, -NO₂, an optionally substituted C1-C5 alkoxy, -CN, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally
20 substituted C2-C5 alkynyl or halogen;

R₃ is H, OH, optionally substituted C1-C10 alkyl, optionally substituted C2-C10 alkenyl, an optionally substituted C2-C10 alkynyl, optionally substituted C1-C10 alkoxy, -OR_{3a}, -OR_{3b}, -SR_{3a}, -SR_{3b}, -N(R_{3a})(R_{3b}), -N(R_{3a})(R_{3a}), -N(R_{3b})(R_{3b}), an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an
25 optionally substituted carbocycle or an optionally substituted heterocycle;

R_{3a} is H or an optionally substituted C1 to C10 alkyl an optionally substituted C2-C10 alkenyl, an optionally substituted C2 – C10 alkynyl or R_{3a} and R_{3b} taken together with the N to which they are attached can form a heterocycle or heteroaryl;

5 R_{3b} is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an optionally substituted carbocycle, an optionally substituted heterocycle, or an optionally substituted C1 to C10 alkyl, an optionally substituted C2-C10 alkenyl, an optionally substituted C2 – C10 alkynyl or R_{3a} and R_{3b} taken together with the N to which they are attached can form a heterocycle or heteroaryl;

10 each of R₄, R₅, R₆ and R₇ are independently: H, a halogen, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, hydroxyl, NO₂, an optionally substituted C1-C5 alkoxy, -CN, -C(O)OH, an optionally substituted -SO₂CH₃, an optionally substituted -SO₂NH₂, an optionally substituted -SO₂OH, -C(O)H, an optionally substituted -C(O)CH₃, an optionally substituted -C(O)N(CH₃)₂, an optionally substituted -C(O)NH₂, an optionally substituted
15 -SCH₃, an optionally substituted heterocycle or heteroaromatic, or -N(R_{2a})(R_{2b});

wherein each R_{2a} and R_{2b} is independently: H, hydroxy, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl; an optionally substituted C2-C5 alkynyl; an optionally substituted C1-C5 alkoxy or an R_{2a} and R_{2b} attached to the same nitrogen, taken together with that nitrogen form an optionally substituted heterocycle or
20 heteroaromatic;

and

each of R₈, R₉, R₁₀, R₁₁ and R₁₂ is independently H, -CN, hydroxyl, a halogen, an optionally substituted C1-C5 alkyl, an optionally substituted C2-C5 alkenyl, an optionally substituted C2-C5 alkynyl, hydroxyl, NO₂, an optionally substituted C1-C5 alkoxy, -
25 N(R_{2a})(R_{2b}), -C(O)OH, an optionally substituted -SO₂CH₃, an optionally substituted -SO₂NH₂, an optionally substituted -SO₂OH, -C(O)H, an optionally substituted -C(O)CH₃, an optionally substituted -C(O)N(CH₃)₂, an optionally substituted -C(O)NH₂, an optionally substituted -SCH₃, an optionally substituted heterocycle or heteroaromatic, or

an R_{1a} attached to a carbon directly bonded to the ring bearing R_8 , taken with R_8 and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle, or an R_{1a} attached to a carbon directly bonded to the ring bearing R_{12} , taken with R_{12} and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl or carbocycle or an optionally substituted heterocycle.

448. The compound of claim 447 wherein R_2 is H

449. The compound of claim 447 wherein R_2 is an optionally substituted C1-C5 alkyl or halogen.

450. The compound of claim 447 wherein R_2 is an optionally substituted methyl.

451. The compound of claim 447 wherein R_2 is halogen.

452. The compound of claim 447 wherein R_2 is F.

453. The compound of claim 447 wherein R_2 is Cl.

454. The compound of claim 447 wherein R_2 is an optionally substituted C1-C5 alkyl.

455. The compound of claim 447 wherein R_2 is methyl.

456. The compound of claim 447 wherein R_2 is selected from optionally substituted C1-C3 alkyl, Cl, and CF_3

457. The compound of claim 447 wherein R_2 is methyl or ethyl.

458. The compound of claim 447 wherein R_2 is Cl or singly or multiply fluorinated methyl or ethyl.

459. The compound of claims 447-458 wherein m is one.

460. The compound of any of claims 447-459 wherein R_{1a} and R_{1b} are both H.

461. The compound of any of claims 447-460 wherein R_{1a} and R_{1b} are both methyl.
462. The compound of any of claims 447-460 wherein the R_{1a} attached to a carbon directly bonded to the ring bearing R_8 , taken with R_8 and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl.
- 5 463. The compound of any of claims 447-460 wherein the attached to a carbon directly bonded to the ring bearing R_{12} , taken with R_{12} and the carbon to which R_{1a} is attached form an optionally substituted C3-C6 cycloalkyl.
464. The compound of any of claims 447-458 wherein m is 1 and R_{1a} and R_{1b} taken together with the carbon to which they are attached form an optionally substituted C3-C6
10 cycloalkyl.
465. The compound of any of claims 447-460 wherein R_{1a} and R_{1b} attached to the same carbon, taken together with that carbon, form an optionally substituted heterocycle.
466. The compound of any of claims 447-465 wherein R_9 and R_{11} are both H.
467. The compound of any of claims 447-466 wherein R_4 is H.
- 15 468. The compound of any of claims 447-467 wherein each of R_4 , R_5 , R_6 , and R_7 is independently selected from H, a halogen, an optionally substituted C1-C5 alkyl, hydroxyl, and an optionally substituted C1-C5 alkoxy.
469. The compound of any of claims 447-468 wherein no more than four of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.
- 20 470. The compound of any of claims 447-469 wherein no more than three of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.
471. The compound of any of claims 447-470 wherein no more than two of R_8 , R_9 , R_{10} , R_{11} and R_{12} are other than H.

472. The compound of any of claims 447-471 wherein only one of R_3 , R_9 , R_{10} , R_{11} and R_{12} is other than H.

473. The compound of any of claims 447-472 wherein R_{3a} is H.

474. The compound of any of claims 447-472 wherein R_{3a} is methyl or ethyl.

5 475. The compound of any of claims 447-472 wherein R_{3b} is an optionally substituted aryl containing a single ring or an optionally substituted heteroaryl containing a single ring.

476. The compound of any of claims 447-472 wherein R_{3b} is an optionally substituted C6 aryl.

10 477. The compound of any of claims 447-472 wherein R_{3b} is an optionally substituted heteroaryl ring containing 6 ring atoms.

478. The compound of any of claims 447-472 wherein R_{3b} is an optionally substituted heteroaryl ring containing 5 ring atoms.

15 479. The compound of any of claims 447-472 wherein R_3 is an optionally substituted heteroaryl.

480. The compound of any of claims 447-472 wherein R_3 is an optionally substituted morpholino.

481. The compound of any of claims 447-472 wherein R_3 is an optionally substituted aryl.

20 482. The compound of any of claims 447-472 wherein R_3 is an optionally substituted C3-C6 cycloalkyl.

483. The compound of any of claims 447-472 wherein R_{3b} is a 6, 5-fused heteroaryl.

484. The compound of any of claims 447-472 wherein R_{3b} is a heteroaryl containing 6 ring atoms of which up to two are N.

485. The compound of any of claims 447-472 where R_3 is $-N(R_{3a})(R_{3b})$, R_{3a} is H and R_{3b} is six-membered heteroaryl containing one or two N.

5 486. The compound of any claims 447-485 wherein any optional substitution is independently selected from: halogen, hydroxy, CN, C1-C3 alkyl, halogen substituted C1-C3 alkyl, C1-C3 alkoxy, and halogen substituted C1-C3 alkoxy.

487. The compound of any of claims 446-486 wherein R_{10} is Cl, an optionally halogen substituted methyl or an optionally halogen substituted methoxy.

10 488. The compound of any of claims 446-487 wherein R_7 is H.

489. The compound of any claims 446-488 wherein R_3 is $-N(H)R_{3b}$.

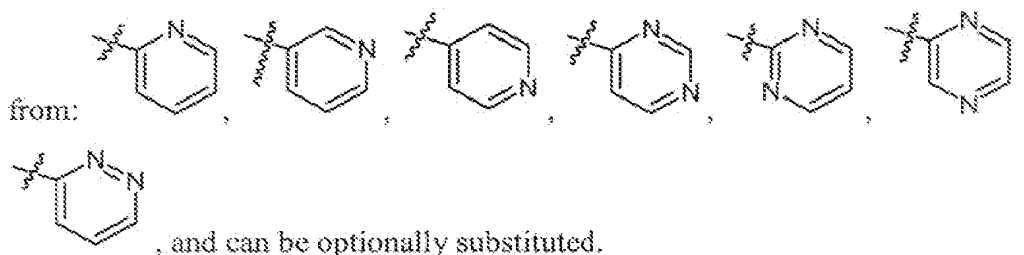
490. The compound of any of claims 446-489 wherein R_5 is an optionally halogen substituted methyl or an optionally halogen substituted methoxy.

15 491. The compound of any of claims 446-490 wherein at least one of R_4 , R_6 , and R_7 is H.

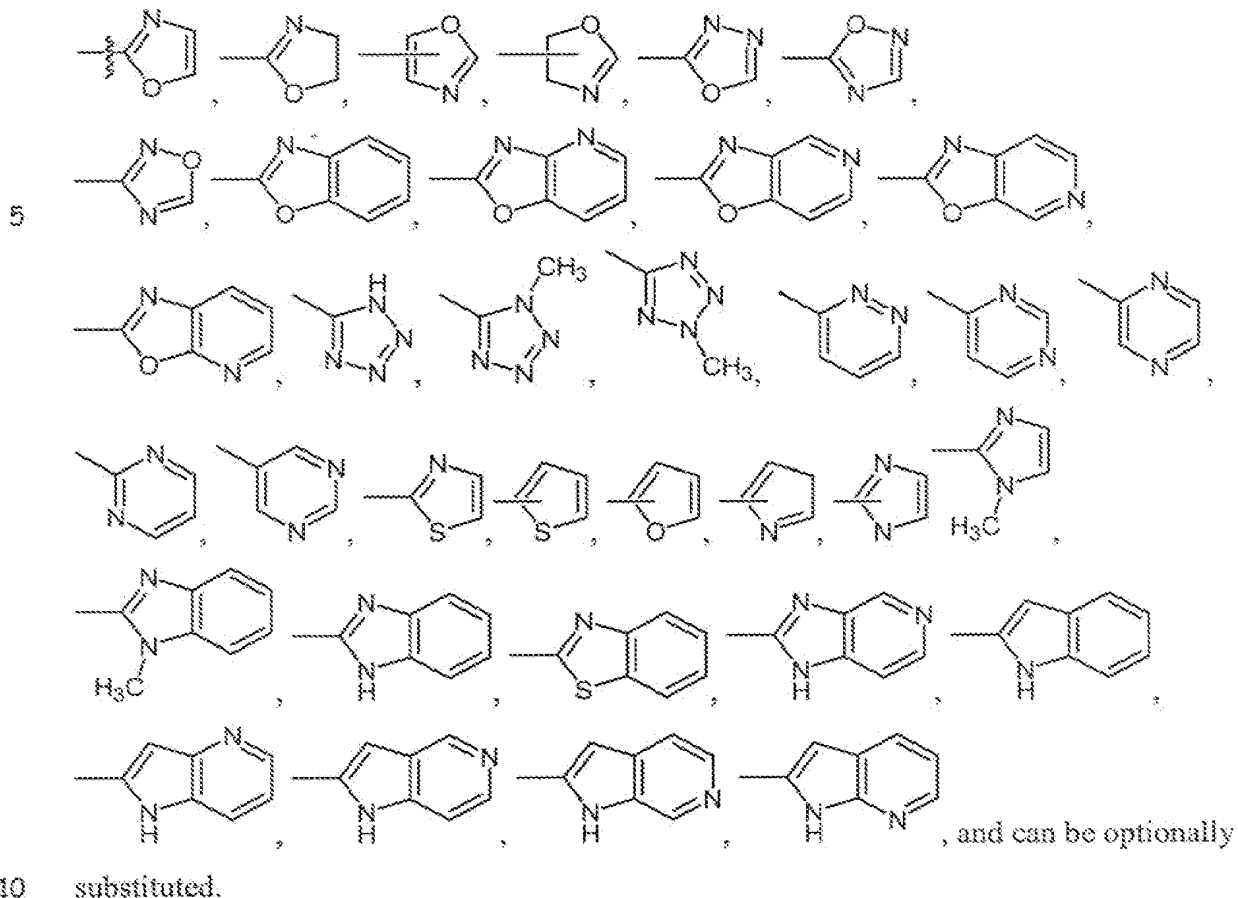
492. The compound of any of claims 446-491 wherein at least two of R_4 , R_6 , and R_7 are H.

493. The compound of any of the claims 446-492 wherein R_4 , R_6 , and R_7 are H.

494. The compound of claim 446 wherein R_{3b} is selected from:



495. The compound of claim 446 wherein R_{3b} is selected from:



496. The compound of any of claims 446-491 wherein R_{3b} is selected from an optionally substituted pyridinyl group, an optionally substituted pyrimidinyl group and an optionally substituted phenyl group.

15 497. The compound of any of claims 446-491 wherein R_{3b} is an optionally substituted pyridinyl group.

498. The compound of any of claims 446-491 wherein R_{3b} is an optionally substituted pyrimidinyl group.
499. The compound of any of claims 446-491 wherein R_{3b} is an optionally substituted phenyl group.
- 5 500. The compound of any of claims 446-499 wherein A is O.
501. The compound of any of claims 446-499 wherein A is NOCH_3 .
502. A compound of any of claims 446-501 wherein R_3 is $-\text{N}(R_{3a})(R_{3b})$.

FIGURE 1

Row	IUPAC name	COX-1 IC50 (μm)	COX-2 IC50 (μm)
1	{6-fluoro-5-methoxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl}acetic acid	3.3	0.29
2	{1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	5	0.2
3	{1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	3.22
4	{6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl}acetic acid	6.3	0.32
5	{6-fluoro-5-hydroxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl}acetic acid	16.3	0.41
6	{6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl}acetic acid	27.3	0.23
7	{1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	35	0.2
8	{1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	85, 90	0.56 0.6
9	{1-[(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>10
10	{1-[(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	2.8
11	{5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl}acetic acid	>100	8.9
12	{5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl}acetic acid	>100	>22.2
13	{1-[(5-chloro-2-thienyl)methyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid	>100	>10%
14	{6-chloro-1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>10%
15	{1-[(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>100
16	{1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>100
17	{1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	3.03
18	{1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	0.4
19	{1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	0.8

FIGURE 2A

Table 2A. CRTH2 agonist assay

ROW	IUPAC name	CD11b agonist activity at 10 uM (%)	CD11b agonist activity at 1 uM (%)
1	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	91.5	100.7
2	[1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	104.1	98
3	[5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid	35.9	45.1
4	[5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid	43.8	40.4
5	[5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid	48.6	35.9
6	[1-(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	35.7	30.1
7	[1-(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	44.8	28.0
8	[1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	30.1	11.9
9	[6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid	49.7	61.5
10	[6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid	44.8	39.9
11	[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	93.0	129.4
12	[6-fluoro-5-hydroxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl]acetic acid	32.2	26.1
13	[6-fluoro-5-methoxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl]acetic acid	46	43.5
14	[4-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	55.3	46.8
15	[6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid	46.8	65.4
16	[6-chloro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	35.3	16.2
17	[6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	34.2	19.3
positive control	[5E,9α,13E,15R]-9,15-dihydroxy-15-methyl-11-oxoprostano-5,13-dien-1-ol-ic acid	95.6	100

FIGURE 2B

Table 2B. CRTH2 antagonist assay

Row	IUPAC name	CRTH2 antagonist activity at 10 μ M (% inhibition)
1	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	92.4
2	(1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	60.4
3	(1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	96.1
4	(1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	104.7
5	(1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	91.2
6	(1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	51.7
7	(1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	60.4
8	(1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	75.2
9	(1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	82.5
10	(1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	91.2
11	(1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	78.9
12	(1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	89.9
13	(1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	96.1
14	(1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	101.0
15	(1-(4-bromobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	92.4
16	(1-(5-chloro-2-thienylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	87.5
17	(1-(5-chloro-2-thienylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	86.2
18	(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	99.8
19	(1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	77.6
20	(1-(4-chlorophenylsulfonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	103.5
21	(1-(4-chlorophenylsulfonyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	103.5
22	(5-methoxy-2-methyl-1-(2E)-3-phenylprop-2-en-1-yl-1H-indol-3-yl)acetic acid	83.8
23	(1-(4-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	48.0
24	(1-(5-chloro-2-thienylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	91.2
25	(5-hydroxy-2-methyl-1-(2E)-3-phenylprop-2-en-1-yl-1H-indol-3-yl)acetic acid	98.8
26	(1-(5-chloro-2-thienylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	57.9
27	(5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl)acetic acid	6.2
28	(5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl)acetic acid	48.8
29	(6-fluoro-5-hydroxy-2-methyl-1-(4-(trifluoromethyl)thiobenzoyl)-1H-indol-3-yl)acetic acid	98.8
30	(5-hydroxy-2-methyl-1-(4-(trifluoromethyl)thiobenzoyl)-1H-indol-3-yl)acetic acid	102.3
31	(6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	73.9
32	(6-fluoro-5-methoxy-2-methyl-1-(5-methyl-2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	69.9
33	(6-fluoro-5-hydroxy-2-methyl-1-(5-methyl-2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	69.9
34	(6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	54.2
35	(6-fluoro-5-hydroxy-2-methyl-1-(4,1,1,2,2-tetrafluoroethoxy)benzoyl)-1H-indol-3-yl)acetic acid	37.0
36	(6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	94.9
37	(5-methoxy-1-(4-methoxybenzoyl)-2-methyl-1H-indol-3-yl)acetic acid	39.4
38	(5-methoxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid	80.1
39	(1-(5-chloro-2-thienylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	60.1
40	(1-(5-chloro-2-thienylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	86.2
41	(6-chloro-5-methoxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid	60.1
42	(1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	98.1
43	(6-chloro-5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid	69.9
44	(6-chloro-1-(5-chloro-2-thienylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	72.7
45	(1-(5-chloro-2-thienylcarbonyl)-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	88.2
46	(5-fluoro-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid	94.9
47	(1-benzoyl-5-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	46.8
48	(1-benzoyl-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	91.2
49	(5-fluoro-1-(4-fluorobenzoyl)-2-methyl-1H-indol-3-yl)acetic acid	98.8
50	(6-chloro-1-(5-chloro-2-thienylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	49
51	(6-chloro-1-(5-chloro-2-thienylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	48.0
positive control	3-((1R)-1-(4-fluorophenyl)sulfonyl)amino-1,2,3,4-tetrahydro-8H-carbazol-8-yl)propanoic acid	88.7, 68.3

FIGURE 3

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (µm)	COX-2 Purified Enzyme Assay IC50 (µm)	COX-1 Human Whole Blood Assay IC50 (µm)	COX-2 Human Whole Blood Assay IC50 (µm)
1	(1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid (CRTH2 antagonist control)	>100	>100		
2	(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid (COX and FAAH control)	0.13, 0.2, 0.1	0.11, 0.1, 0.15, 1.1	0.14, 0.14, 0.22, 0.22	0.25, 0.25, 0.2, 0.2
3	3-((3R)-5-((4-fluorophenyl)sulfonyl)amino)-1,2,3,4-tetrahydro-9H-pyrazolo[5,4-b]pyridine-2-carboxylic acid (CRTH2 control)	>100	>100		
4	3-(aminocarbonyl)biphenyl-3-yl cyclohexylcarbamate (FAAH control)				
5	4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (COX control)	>100	0.045	100	0.15
6	4-(4-(methanesulfonyl)phenyl)-3-phenylfuran-2(5H)-one (COX control)	>100	3.2	39	0.24
7	4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (COX control)	15, 12	0.22, 0.17	11.3, 11.3, 12.2, 12.8	0.40, 0.40, 0.45, 0.42
8	5-benzoyl-2,3-dihydro-1H-pyridine-1-carboxylic acid (FAAH control)				
9	indole-2-carboxylic acid (DAO control)				
10	(5-methoxy-2-methyl-1-(4-(trifluoromethyl)benzoyl)-1H-indol-3-yl)acetic acid	16.8	0.4		
11	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	3	0.3		
12	(1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0.3	0.22		
13	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>10		
14	(5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
15	(1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
16	(1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	20.4	7.1		
17	(1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	50	4		
18	(1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	8.5, 10, 9.4	0.15, 0.2, 0.20, 0.13	12.9	0.51
19	(1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	60	>10		
20	(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid				
21	(1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0.6	0.4		
22	(1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
23	(1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	0.8		

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (µm)	COX-2 Purified Enzyme Assay IC50 (µm)	COX-1 Human Whole Blood Assay IC50 (µm)	COX-2 Human Whole Blood Assay IC50 (µm)
24	1-((4-chlorophenyl)sulfonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100, >100	>10, >10		
25	1-((5-chloro-2-thienyl)carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	5	0.2		
26	1-((6-chloropyridin-3-yl)carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	2.8		
27	1-((5-hydroxy-2-methyl-1-(2E)-3-phenylprop-2-en-1-yl)-1H-indol-3-yl)acetic acid	0.1	>8		
28	1-((5-methoxy-2-methyl-1-(2E)-3-phenylprop-2-en-1-yl)-1H-indol-3-yl)acetic acid	0.1	5.45		
29	2-((2-hydroxyethyl)acetamide)-1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-(2-phenylethyl)acetamide	>100	>10		
30	2-((2-hydroxyethyl)acetamide)-1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-(2-phenylethyl)acetamide	>100	4.81	>100	>100
31	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	12.9	11.48	90.93	1.8
32	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	36.9, >100	>50, >50		
33	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	8.6	>10	61.6	>100
34	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>10		
35	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>10		
36	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>10		
37	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>10		
38	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	0.33, 0.26		
39	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	10.5	0.35		
40	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
41	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
42	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
43	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
44	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
45	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>10, >100	>100, >10		
46	1-((4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>10	>10		

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (µm)	COX-2 Purified Enzyme Assay IC50 (µm)	COX-1 Human Whole Blood Assay IC50 (µm)	COX-2 Human Whole Blood Assay IC50 (µm)
47	(6-fluoro-5-methoxy-2-methyl-1,4-(trifluoromethyl)thio)benzyl-1H-indol-3-ylacetic acid	100	>100		
48	(1-(1,3-benzothiazol-2-ylmethyl)-4-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid				
49	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl)acetic acid	>100	>100		
50	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid				
51	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100, >100, >10	>100, >100, >10		
52	(1-(1,3-benzothiazol-2-ylmethyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>10, >100	>100, >10		
53	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid				
54	(1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
55	(1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
56	(1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	29.9	>10		
57	(1-(2-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		>100
58	(1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
59	(1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
60	(1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
61	(1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
62	(1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
63	(1-(4-bromobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	21.1, 26.3	0.18, 0.16	60.9	0.67
64	(1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	2.2	0.14		
65	(1-(4-bromobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
66	(1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	24.6	>10		
67	(1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
68	(1-(4-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	10	>100		
69	(1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	<10			<10

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (µm)	COX-2 Purified Enzyme Assay IC50 (µm)	COX-1 Human Whole Blood Assay IC50 (µm)	COX-2 Human Whole Blood Assay IC50 (µm)
70	[1-(4-chlorobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
71	[1-(4-chlorobenzoyl)-4-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100, >100	1.3, 4.3	59.7	8
72	[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	30, 30, 31.5	0.5, 0.5, 0.23, 0.27, 0.15	28.8, 30.2	0.79, 0.60
73	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	5, 2.3	1.5, 0.6		
74	[1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
75	[1-(4-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	72	2.7		
76	[1-(4-ethylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0.2	>10		
77	[1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	14	0.9		
78	[1-(4-tert-butylbenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
79	[1-(biphenyl-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
80	[1-(biphenyl-4-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
81	[1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	3.03		
82	[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	3.22		
83	[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	0.4		
84	[3-(1,3-benzothiazol-2-ylmethyl)-1H-indol-1-yl]acetic acid				
85	[4-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>30		
86	[4-chloro-1-(4-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	10	>100		>100
87	[5-fluoro-1-(4-fluorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
88	[5-hydroxy-2-methyl-1-(3-methylbenzoyl)-1H-indol-3-yl]acetic acid	>100 ND	>10		
89	[5-hydroxy-2-methyl-1-(3-phenylprop-2-ynyl)-1H-indol-3-yl]acetic acid	4.9	>10		
90	[5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid	0.45	0.3		
91	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	>100	8.9		
92	[5-methoxy-1-(4-methoxybenzoyl)-2-methyl-1H-indol-3-yl]acetic acid	31.9	>100		

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (µm)	COX-2 Purified Enzyme Assay IC50 (µm)	COX-1 Human Whole Blood Assay IC50 (µm)	COX-2 Human Whole Blood Assay IC50 (µm)
93	5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-ylacetic acid	>100	>22.2		
94	[6-chloro-1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
95	[6-chloro-1-(2,5-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
96	[6-chloro-1-(2,6-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
97	[6-chloro-1-(2-chloro-4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>10, >100	>10, >100		
98	[6-chloro-1-(2-chloro-6-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
99	[6-chloro-1-(2-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	100	>100		
100	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
101	[6-chloro-1-(3-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	>10, 4.7	>100, >100		
102	[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid				
103	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	10, 72.0	>10, >100		
104	[6-chloro-1-(3-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
105	[6-chloro-1-(3-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>10	>100		
106	[6-chloro-1-(4-chloro-2-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
107	[6-chloro-1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	100, >100	>10, >100	>100	>100
108	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	1.7		
109	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	20.2, 18.8, 30, 47.7	0.31, 0.15, 3.3, 0.1	14	0.43
110	[6-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	>10	>100		>100
111	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
112	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	16.1, >100, >100, 30.4	>10, >100, >10, >100		
113	[6-chloro-1-(4-chlorophenyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100			>100
114	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	0.21, 0.37		
115	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (μm)	COX-2 Purified Enzyme Assay IC50 (μm)	COX-1 Human Whole Blood Assay IC50 (μm)	COX-2 Human Whole Blood Assay IC50 (μm)
116	(6-chloro-1-(cyclohexylmethyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
117	(6-chloro-5-methoxy-1-(3-methoxybenzyl)-2-methyl-1H-indol-3-yl)acetic acid				
118	(6-chloro-5-methoxy-2-methyl-1-(2-naphthylmethyl)-1H-indol-3-yl)acetic acid				
119	(6-chloro-5-methoxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl)acetic acid	>10	>100		
120	(6-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylmethyl)-1H-indol-3-yl)acetic acid				
121	(6-chloro-5-methoxy-2-methyl-1-(quinolin-2-ylmethyl)-1H-indol-3-yl)acetic acid	>10, >100	>100, >10		
122	(6-fluoro-1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100	0.18	26.6	0.63
123	(6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	8.2	0.13	3.1	0.36
124	(6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>10			>100
125	(6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	27.3	0.23	14.5	0.2
126	(6-fluoro-5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl)acetic acid	3.6	0.27		
127	(6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	6.3	0.32		
128	(6-fluoro-5-methoxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl)acetic acid	1	0.13		
129	(1-(4-chlorophenyl)sulfonyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>10		
130	(1-(4-chlorophenyl)sulfonyl-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100, >10	>100, >100		
131	(1-(5-chloro-2-thienyl)carbonyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	5.5	0.5		
132	(1-(5-chloro-2-thienyl)carbonyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	85, 90	0.56, 0.6	36	0.86
133	(1-(5-chloro-2-thienyl)carbonyl-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	35	0.2	7.1	0.48
134	(1-(5-chloro-2-thienyl)methyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>10		
135	(1-(5-chloro-2-thienyl)methyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
136	(1-(5-chloro-2-thienyl)methyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
137	(1-(6-chloropyridin-3-yl)carbonyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100 ND	>10		
138	(1-(4-difluoromethoxy)benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	45	0.25	67.43	0.63

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (μm)	COX-2 Purified Enzyme Assay IC50 (μm)	COX-1 Human Whole Blood Assay IC50 (μm)	COX-2 Human Whole Blood Assay IC50 (μm)
139	1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-ylacetic acid	4.9	0.56		
140	1-[4-(difluoromethoxy)benzoyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid	>100	0.2	71	0.85
141	1-[4-(difluoromethoxy)benzoyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid	18.1	0.1	12.2	0.19
142	1-[4-(difluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	>10		
143	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	40		
144	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	>100		
145	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	25	>100		
146	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	0.2	21.5	0.6
147	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	>100		
148	1-[4-(chlorophenoxy)carbonyl]-5-methoxy-2-methyl-1H-indol-3-ylacetic acid				
149	1-[4-(chlorophenoxy)carbonyl]-5-fluoro-2-methyl-1H-indol-3-ylacetic acid	>10	>10		
150	1-[4-(chlorophenoxy)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid	>10	>10		
151	1-[4-(chlorophenoxy)carbonyl]-5-methoxy-2-methyl-1H-indol-3-ylacetic acid	>100, 71.3	>10, >100		
152	1-[4-(chlorophenoxy)carbonyl]-5-methoxy-2-methyl-1H-indol-3-ylacetic acid	>100	>10		
153	1-[4-(chlorophenoxy)carbonyl]-5-methoxy-2-methyl-1H-indol-3-ylacetic acid	>10	>100		
154	1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-ylacetic acid	>100, >100	0.28, 0.67	54.33	0.66
155	1-[4-(difluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	>100		
156	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	>100		
157	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid				
158	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	>100		
159	1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-ylacetic acid	>100	>100		
160	1-[4-(methoxycarbonyl)benzoyl]-2-methyl-1H-indol-3-ylacetic acid	>100	>100		
161	1-[4-(methoxycarbonyl)benzoyl]-2-methyl-1H-indol-3-ylacetic acid	>100	>100		>100

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (µm)	COX-2 Purified Enzyme Assay IC50 (µm)	COX-1 Human Whole Blood Assay IC50 (µm)	COX-2 Human Whole Blood Assay IC50 (µm)
162	(6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acetic acid	>100	>100		
163	(6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid	>10, 12.8, 4.5	>100, >100		
164	(6-chloro-5-methoxy-2-methyl-1-[4-(methylsulfonyl)benzyl]-1H-indol-3-yl)acetic acid	>100	>100		
165	(trifluoromethoxy)benzoyl-1H-indol-3-ylacetic acid	>100	>100	>100	>100
166	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acetic acid	24.9, >10	>100, >100		>100
167	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid	>10	>10		
168	(6-fluoro-5-hydroxy-2-methyl-1-[5-methyl-2-thienyl]carbonyl)-1H-indol-3-ylacetic acid	16.3	0.41		
169	(6-fluoro-5-hydroxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl)acetic acid	0.3	0.36		
170	(6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid	>100	>8		
171	(6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl)acetic acid	>100	>8		
172	(6-fluoro-5-methoxy-2-methyl-1-[5-methyl-2-thienyl]carbonyl)-1H-indol-3-ylacetic acid	3.3	0.29		
173	(6-fluoro-5-methoxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl)acetic acid	0.2	0.06		
174	(6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid	>100, >100	0.59, 0.31, 0.4	41.8	0.35
175	(6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl)acetic acid	76.2, 95	0.37, 0.45	27.2	0.6
176	2-(trimethylsilyl)ethyl (6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetate	>100	>10		
177	2-(trimethylsilyl)ethyl 1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-ylacetate				
178	2-(trimethylsilyl)ethyl 1-(5-chloro-2-thienyl)carbonyl-6-fluoro-5-methoxy-2-methyl-1H-indol-3-ylacetate				
179	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]N-piperidin-1-ylacetamide				
180	3-ylacetamide	>100	>10		
181	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl acetate	>100	>10		
182	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl acetate	>100	>10		
183	3-[1-(1,3-benzothiazol-2-ylmethyl)-4,6-dichloro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		
184	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl]propanoic acid	>100	>100		

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (µm)	COX-2 Purified Enzyme Assay IC50 (µm)	COX-1 Human Whole Blood Assay IC50 (µm)	COX-2 Human Whole Blood Assay IC50 (µm)
185	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		
186	3-[4,6-dichloro-1-(3-chlorobenzyl)-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		
187	3-[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		
188	3-[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		>100
189	4-[3-(carboxymethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-1-yl]methylbenzoic acid	<10	>10		
190	1-ylmethylbenzoic acid	21.3	7.98		
191	ethyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	33	5.98		
192	ethyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10	>100	>100
193	ethyl [6-chloro-1-(4-(difluoromethoxy)benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
194	ethyl 4-[(1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetyl]amino butanoate	>100	>50		
195	ethyl N-[(1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetyl]glycinate	>100	>10		
196	ethyl N-[(6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl]glycinate			>100	>100
197	isopropyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	11	0.66		
198	methyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	15, 16	>10, >100		
199	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	30.1, 45.1	8.38, 18.53		
200	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
201	methyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100, >100	>10, >100		
202	methyl N-[(1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetyl]-L-alaninate	>100	>10		
203	N-[(6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl]glycine	>100	>100		
204	propyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	5.3	8.41		
205	propyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	28	5.79		
206	propyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
207	sec-butyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	>100	>50		

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (µm)	COX-2 Purified Enzyme Assay IC50 (µm)	COX-1 Human Whole Blood Assay IC50 (µm)	COX-2 Human Whole Blood Assay IC50 (µm)
208	sec-butyl [6-chloro-1-(4-chloro benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
209	sec-butyl [6-chloro-1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10 μ M (percent inhibition)	CD11b agonist activity at 10 μ M (percent activation)
1	[1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid (CRTH2 antagonist control)		10		
2	[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid (COX and FAAH control)				
3	3-((3R)-3-((4-fluorophenyl)sulfonylamino)-1,2,3,4-tetrahydro-9H-carbazol-9-yl)propanoic acid (CRTH2 control)		49.0, 16.0, 2.5, 22	87	-12.5
4	3-(aminocarbonyl)biphenyl-3-yl cyclohexylcarbamate (FAAH control)				
5	4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (COX control)	>100, 000			
6	4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (COX control)	>100, 000			
7	4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (COX control)				
8	5-benzoyl-2,3-dihydro-1H-pyrazol-1-carboxylic acid (FAAH control)				
9	indole-2-carboxylic acid (DAO control)				
10	[5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid				48.6
11	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid				
12	(1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid				
13	(1-benzyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100, 000	1007	92.4	-9.5
14	(5-fluoro-2-methyl-1H-indol-3-yl)acetic acid				
15	[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		226.0, 205.3	96.1	-2.628
16	[1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		234	96.1	
17	[1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				104.1
18	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
19	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 100 μ M			
20	[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		103.8	99.8	
21	[1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
22	[1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			77.6	
23	[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			51.7	0.9

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10 μ M (percent inhibition)	CD11b agonist activity at 10 μ M (percent activation)
24	(1-(4-chlorophenyl)sulfonyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		2135.0, 70.96	103.5	-5.4
25	(1-(5-chloro-2-thienyl)carbonyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		11	87.5	-0.4
26	(1-(6-chloropyridin-3-yl)carbonyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid				
27	(5-hydroxy-2-methyl-1-(2E)-3-phenylprop-2-en-1-yl-1H-indol-3-yl)acetic acid		105.1	98.6	
28	(5-methoxy-2-methyl-1-(2E)-3-phenylprop-2-en-1-yl-1H-indol-3-yl)acetic acid		26.94	83.8	
29	(2-hydroxyethyl)acetamide				
30	(2-phenylethyl)acetamide				
31	(2-(1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)ethanol				
32	ethyl 1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetate				
33	ethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-ylacetate				
34	ethyl N-((1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate)glycidate				
35	N-((1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate)glycidine				
36	(6-fluoro-5-hydroxy-2-methyl-1-(4-(1,1,2,2-tetrafluoroethoxy)benzoyl)-1H-indol-3-yl)acetic acid"			37	32.2, 46.8
37	(6-fluoro-5-methoxy-2-methyl-1-(4-(1,1,2,2-tetrafluoroethoxy)benzoyl)-1H-indol-3-yl)acetic acid"				46
38	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid			46.8	29.1
39	(1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid			60.4	
40	(1-benzyl-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid		166.0, 126.0	91.2	6-9.5
41	(1-benzyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		20, 21.4		
42	(5-chloro-1-((4-chlorophenyl)amino)carbonyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		114		
43	(6-chloro-5-methoxy-2-methyl-1-(4-(trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid		2300		
44	(6-chloro-5-methoxy-2-methyl-1-(4-(trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid		84		
45	(6-fluoro-5-hydroxy-2-methyl-1-(4-(trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid				
46	(6-fluoro-5-methoxy-2-methyl-1-(4-(trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid		54.0, 41.0, 29.0, 14.5	99.8	-10.5

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10 μ M (percent inhibition)	CD11b agonist activity at 10 μ M (percent activation)
47	(6-fluoro-5-methoxy-2-methyl-1-(4- (trifluoromethyl)thio)benzyl)-1H-indol-3-yl)acetic acid		286		
48	(1-(1,3-benzothiazol-2-ylmethyl)-4-chloro-5-methoxy-2- methyl-1H-indol-3-yl)acetic acid		734		
49	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H- indol-3-yl)acetic acid		2.0, 6.0		
50	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl- 1H-indol-3-yl)acetic acid				
51	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2- methyl-1H-indol-3-yl)acetic acid		38.0, 38.0, 10, 13		
52	(1-(1,3-benzothiazol-2-ylmethyl)-6-fluoro-5-methoxy-2- methyl-1H-indol-3-yl)acetic acid		98		
53	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl- 1H-indol-3-yl)acetic acid		151		
54	(1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3- yl)acetic acid			75.2	
55	(1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3- yl)acetic acid			60.4	
56	(1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3- yl)acetic acid		177	91.2	9
57	(1-(2-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3- yl)acetic acid		187		
58	(1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3- yl)acetic acid		181.0, 120.4	104.7	-1.2-9.5
59	(1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3- yl)acetic acid		151.9	89.9	-0.3
60	(1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3- yl)acetic acid			78.9	
61	(1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid		647	91.2	-2.3
62	(1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3- yl)acetic acid	>100, 000	114	82.5	
63	(1-(4-bromobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3- yl)acetic acid	26			
64	(1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol- 3-yl)acetic acid				
65	(1-(4-bromobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol- 3-yl)acetic acid		109.0, 47.0	92.4	0.8
66	(1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H- indol-3-yl)acetic acid				
67	(1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid		396.0, 408.1	101	-7.4
68	(1-(4-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3- yl)acetic acid		100		
69	(1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3- yl)acetic acid		50		

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10 μ M (percent inhibition)	CD11b agonist activity at 10 μ M (percent activation)
70	[1-(4-chlorobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
71	[1-(4-chlorobenzoyl)-4-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
72	[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
73	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				91.5
74	[1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		113.0, 530.0	96.1	4.9-0.3
75	[1-(4-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			48	
76	[1-(4-ethylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
77	[1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
78	[1-(4-tert-butylbenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		364		
79	[1-(6-phenyl-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
80	[1-(6-phenyl-4-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		126.0, 205.0		
81	[1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
82	[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
83	[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		171	91.2	
84	[3-(1,3-benzothiazol-2-ylmethyl)-1H-indol-1-yl]acetic acid		23, 95		
85	[4-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 10 μ M			55.3
86	[4-chloro-1-(4-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		78		
87	[5-fluoro-1-(4-fluorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid		>100, 23.02	98.6	1.9-28.9
88	[5-hydroxy-2-methyl-1-(3-methylbenzoyl)-1H-indol-3-yl]acetic acid				
89	[5-hydroxy-2-methyl-1-(3-phenylprop-2-ynoyl)-1H-indol-3-yl]acetic acid		806.8	102.3	
90	[5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid				
91	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid			46.8	0.4
92	[5-methoxy-1-(4-methoxybenzoyl)-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 100 μ M		39.4	3.2

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10 μ M (percent Inhibition)	CD11b agonist activity at 10 μ M (percent activation)
93	[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid			6.2	0.4
94	[6-chloro-1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		20, 95.0		
95	[6-chloro-1-(2,5-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
96	[6-chloro-1-(2,6-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		468.0, 722.0, 126.0		
97	[6-chloro-1-(2-chloro-4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		80.0, 499.0		
98	[6-chloro-1-(2-chloro-6-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		97.0, 171		
99	[6-chloro-1-(2-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		48.0, 38, 16.9		
100	[6-chloro-1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		555		
101	[6-chloro-1-(3-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		9.0, 13.0		
102	[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		26.0, 39.0		
103	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		9.0, 33.0, 7.7, 19.0		
104	[6-chloro-1-(3-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		26.0, 47.0		
105	[6-chloro-1-(3-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		32.0, 72.5		
106	[6-chloro-1-(4-chloro-2-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		94		
107	[6-chloro-1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	20			
108	[6-chloro-1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
109	[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	66			
110	[6-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		16.0, 31.0, 32.0, 33.0		
111	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		75.0, 37.0		
112	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		94.0, 32.7, 43.0, 40.0	94.9	6.3-4.3
113	[6-chloro-1-(4-chlorophenyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		Partial Agonist @10 μ M		
114	[6-chloro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				35.3
115	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		52		

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10 μ M (percent inhibition)	CD11b agonist activity at 10 μ M (percent activation)
116	[6-chloro-1-(cyclohexylmethyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		106		
117	[6-chloro-5-methoxy-1-(3-methoxybenzyl)-2-methyl-1H-indol-3-yl]acetic acid		53.4		
118	[6-chloro-5-methoxy-2-methyl-1-(2-naphthylmethyl)-1H-indol-3-yl]acetic acid				
119	[6-chloro-5-methoxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid		16.0, 37.0		
120	[6-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylmethyl)-1H-indol-3-yl]acetic acid		561		
121	[6-chloro-5-methoxy-2-methyl-1-(quinolin-2-ylmethyl)-1H-indol-3-yl]acetic acid		63.0, 212.0		
122	[6-fluoro-1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 10 μ M			
123	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
124	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		238		
125	[6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	>100, 000		54.2	2.1
126	[6-fluoro-5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid				
127	[6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid			73.9	-0.4
128	[6-fluoro-5-methoxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid				
129	[1-(4-chlorophenyl)sulfonyl-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		384.0, 203.0	103.5	-9.5
130	[1-(4-chlorophenyl)sulfonyl-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		278		
131	[1-(5-chloro-2-thienyl)carbonyl-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		173	86.2	0.4
132	[1-(5-chloro-2-thienyl)carbonyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100, 000	86		
133	[1-(5-chloro-2-thienyl)carbonyl-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			57.9	23.2
134	[1-(5-chloro-2-thienyl)methyl-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		61.9	86.2	14.1 -1.3
135	[1-(5-chloro-2-thienyl)methyl-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 100 μ M	172.1	86.2	10.5, 4.9
136	[1-(6-chloropyridin-3-yl)carbonyl-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100, 000		80.1	13.9
137	[1-(4-(difluoromethoxy)benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				
138	[1-(4-(difluoromethoxy)benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 10 μ M			

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10 μ M (percent inhibition)	CD11b agonist activity at 10 μ M (percent activation)
139	(1-(4-(difluoromethoxy)benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid				
140	(1-(4-(difluoromethoxy)benzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	787			
141	(1-(4-(difluoromethoxy)benzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	450			
142	(5-fluoro-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid		142.0, 49.0	94.9	0.5-0.3
143	(5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid				35.9
144	(5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid				
145	(5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid				43.8
146	(5-methoxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid	>1000			
147	(5-methoxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid	partial agonist at 100 μ M		80.1	3.9
148	(6-chloro-1-(4-chlorophenoxy)carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		>10000		
149	(6-chloro-1-(5-chloro-2-thienyl)carbonyl)-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid		95		
150	(6-chloro-1-(5-chloro-2-thienyl)carbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid		1848		
151	(6-chloro-1-(5-chloro-2-thienyl)carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid			48	34.2, 29.1
152	(6-chloro-1-(5-chloro-2-thienyl)methyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		321	72.7	8.9
153	(6-chloro-1-(6-chloropyridin-3-yl)methyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		393		
154	(6-chloro-1-(4-(difluoromethoxy)benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	1000			
155	(6-chloro-2,5-dimethyl-1-(3-(trifluoromethoxy)benzyl)-1H-indol-3-yl)acetic acid				
156	(6-chloro-2,5-dimethyl-1-(3-(trifluoromethyl)benzyl)-1H-indol-3-yl)acetic acid				
157	(6-chloro-5-fluoro-2-methyl-1-(3-(trifluoromethoxy)benzyl)-1H-indol-3-yl)acetic acid				
158	(6-chloro-5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid				
159	(6-chloro-5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl)acetic acid		112.1	89.9	-0.4-2.3
160	(6-chloro-5-methoxy-1-(4-(methoxycarbonyl)benzyl)-2-methyl-1H-indol-3-yl)acetic acid		101.0, 128.0		
161	(6-chloro-5-methoxy-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)methyl)-1H-indol-3-yl)acetic acid		101		

Row	IUPAC Name	CD11B Agonist Assay EC ₅₀ (nM)	CD11B Antagonist Assay IC ₅₀ (nM)	CD11b Antagonist Activity at 10 μ M (percent inhibition)	CD11b agonist activity at 10 μ M (percent activation)
162	(6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acetic acid		4.0, 6.0		
163	(6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid		4.0, 9.0		
164	(6-chloro-5-methoxy-2-methyl-1-[4-(methylsulfonyl)benzyl]-1H-indol-3-yl)acetic acid		1000		
165	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid				46.8
166	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acetic acid		102	80.1	6.3
167	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid		110		
168	(6-fluoro-5-hydroxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl)acetic acid		393.4	89.9	-0.4
169	(6-fluoro-5-hydroxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl)acetic acid				
170	(6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid				
171	(6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl)acetic acid				
172	(6-fluoro-5-methoxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl)acetic acid		466.1	89.9	3.8
173	(6-fluoro-5-methoxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl)acetic acid				
174	(6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid	~100			
175	(6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl)acetic acid	478			
176	2-(trimethylsilyl)ethyl (6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetate				
177	2-(trimethylsilyl)ethyl 1-[4-bromobenzoyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-ylacetate				
178	2-(trimethylsilyl)ethyl 1-[5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetate				
179	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-piperidin-1-ylacetamide		>10000		
180	2-[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetamide				
181	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl 4-chlorobenzoate				
182	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl acetate				
183	3-[1-(1,3-benzothiazol-2-ylmethyl)-4,6-dichloro-2-methyl-1H-indol-3-yl]propionic acid				
184	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl]propionic acid				

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10µM (percent inhibition)	CD11b agonist activity at 10 µM (percent activation)
185	3-(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl)propanoic acid				
186	3-(4,6-dichloro-1-(3-chlorobenzyl)-2-methyl-1H-indol-3-yl)propanoic acid				
187	3-(6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl)propanoic acid				
188	3-(6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)propanoic acid		31.0, 175.0, 209.0, 176.0		
189	4-(3-(carboxymethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)propanoic acid		>10000		
190	butyl 1-(1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetate				
191	ethyl 1-(1-(4-chlorobenzyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetate	>1000			
192	ethyl 6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-ylacetate				
193	ethyl 6-chloro-1-(4-(difluoromethoxy)benzoyl)-5-methoxy-2-methyl-1H-indol-3-ylacetate				
194	ethyl 4-((1-(4-chlorobenzyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetamido)butanoate				
195	ethyl N-((1-(4-chlorobenzyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetamido)llysinate				
196	ethyl N-((6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetamido)llysinate				
197	isopropyl 1-(4-chlorobenzyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetate				
198	ethyl 1-(1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetate	>1000			
199	ethyl 1-(1-(4-chlorobenzyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetate	>1000			
200	indol-3-ylacetate				
201	indol-3-ylacetate				
202	indol-3-ylacetate				
203	indol-3-ylacetate				
204	indol-3-ylacetate				
205	indol-3-ylacetate				
206	indol-3-ylacetate				
207	indol-3-ylacetate				

Row	IUPAC Name	CD11B Agonist Assay EC50 (nM)	CD11B Antagonist Assay IC50 (nM)	CD11b Antagonist Activity at 10 μ M (percent inhibition)	CD11b agonist activity at 10 μ M (percent activation)
208	sec-butyl [6-chloro-1-[4-(chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				
209	sec-butyl [6-chloro-1-[4-(difluoromethoxybenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µM)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µM)
1	[1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid (CRTH2 antagonist control)			-21.3	
2	[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid (COX and FAAH control)	80.15, 77.08, 114 ± 55.5, 150 ± 82		-20.3	
3	3-((3R)-3-((4-fluorophenyl)sulfonylamino)-1,2,3,4-tetrahydro-9H-carbazol-9-yl)propanoic acid (CRTH2 control)		-7	-29	
4	3-(aminocarbonyl)phenyl-3-yl cyclohexylcarbamate (FAAH control)	0.05, 0.04 ± 0.01, 0.13 ± 0.04			
5	4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (COX control)	37.76, 23 ± 3, 21.7 ± 2, 32 ± 2, 33 ± 3		-19.3	
6	4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (COX control)	>300 ± NA, 161 ± 34, 152.3 ± 49, 110.5 ± 9		-52.5	
7	4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (COX control)	36.25, 19.7, 47.7 ± 22.5, 89 ± 25.5		-10.2 -24.4	
8	5-benzoyl-2,3-dihydro-1H-pyrrrolizine-1-carboxylic acid (FAAH control)	63.7 ± 4.5, 106 ± 13, 86 ± 29			
9	indole-2-carboxylic acid (DAO control)			96	0.71, 0.62, 0.49
10	[5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid		22.67	19.5	
11	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid		7.39	30	
12	(1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		16.93	-2.4	
13	(1-benzyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid		-19.63 -11.35	36.3 47.8	5.86
14	(5-fluoro-2-methyl-1H-indol-3-yl)acetic acid			-28	
15	[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		18.88	-9.9	
16	[1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		15.17	-15.7	
17	[1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		17.39	-5.5	
18	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	161 ± NA		22.4	
19	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		20.8	40.3	2.56
20	[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		21	-19.6	
21	[1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		21.93	-40.9	
22	[1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		18.2	-62.8	
23	[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		21.71, 25.49	-15.8	

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µm)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µm)
24	{1-(4-chlorophenyl)sulfonyl}-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		15.0, 15.29	-16.7	
25	{1-(5-chloro-2-thienyl)carbonyl}-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		-13	-14.4	
26	{1-(6-chloropyridin-3-yl)carbonyl}-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		21.58	-18.9	
27	{5-hydroxy-2-methyl-1-[(2E)-3-phenylprop-2-en-1-yl]-1H-indol-3-yl}acetic acid		2.16	-24.2	
28	{5-methoxy-2-methyl-1-[(2E)-3-phenylprop-2-en-1-yl]-1H-indol-3-yl}acetic acid		16	-66.7	
29	{2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-hydroxyethyl)acetamide}			-77.7	
30	{2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-phenylethyl)acetamide}	>300 ± NA		0.7	
31	{2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethanol}	3.69		-59.9	
32	ethyl {1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl}acetate			-40.9	
33	ethyl {1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl}acetate			-43.4	
34	ethyl N-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	208 ± 31		-50.7	
35	N-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	139 ± 8.5		-60.2	
36	{6-fluoro-5-hydroxy-2-methyl-1-[4-(1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl}acetic acid"		3.07, 18.55	23.5	
37	"{6-fluoro-5-methoxy-2-methyl-1-[4-(1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl}acetic acid"		15.32	-27.4	
38	{(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid}	106.5	30.86 -3.75	-34.4	
39	{(1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid}		13.43	39.2	38.1
40	{(1-benzyl-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid}		2.59	-8.3	
41	{(1-benzyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid}			5.8	
42	{(6-chloro-1-[(4-chlorophenyl)amino]carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid			-3.25	
43	{(6-chloro-5-methoxy-2-methyl-1-(4-(trifluoromethyl)thiol)benzoyl)-1H-indol-3-yl}acetic acid			-16.1	
44	{(6-chloro-5-methoxy-2-methyl-1-(4-(trifluoromethyl)thiol)benzoyl)-1H-indol-3-yl}acetic acid		21.54	-33	
45	{(6-fluoro-5-hydroxy-2-methyl-1-(4-(trifluoromethyl)thiol)benzoyl)-1H-indol-3-yl}acetic acid		-10	26.6	
46	{(6-fluoro-5-methoxy-2-methyl-1-(4-(trifluoromethyl)thiol)benzoyl)-1H-indol-3-yl}acetic acid		15.59	-5.2	

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µM)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µM)
47	(6-fluoro-5-methoxy-2-methyl-1-(4-(trifluoromethyl)thiobenzyl)-1H-indol-3-yl)acetic acid		26.26	-48	
48	1-(1,3-benzothiazol-2-ylmethyl)-4-chloro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid			2.99	
49	1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-ylacetic acid			-31.52	
50	1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-ylacetic acid				
51	1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid		25.69	-17.5	
52	1-(1,3-benzothiazol-2-ylmethyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid			-63.5	
53	1-(1,3-benzoxazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid			-12.92	
54	1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid		10.94	-1.9	
55	1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-ylacetic acid		16.77, 31.08	-31.2	
56	1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid		7.49, 25.9	0.3	
57	1-(2-chlorobenzyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid			12.02	
58	1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid		16.87	21.7, 14.6	
59	1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid		8.38	28.6	
60	1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-ylacetic acid		10.01	-52.4	
61	1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid		5.75	15.5	
62	1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-ylacetic acid		7.76	-23	
63	1-(4-bromobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid		14.07	0.9	
64	1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid		23.87	7	
65	1-(4-bromobenzyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid		18	36.7	2.92
66	1-(4-bromobenzyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid		29.09-9.6	-16.8	
67	1-(4-bromobenzyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetic acid		21.78	49.6	1.23
68	1-(4-bromobenzyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid				
69	1-(4-bromobenzyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-ylacetic acid			-19.09	

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µM)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µM)
70	[1-(4-chlorobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		21.05	0.9	
71	[1-(4-chlorobenzoyl)-4-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		18.04	30.6, 38.3	46.84
72	[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	59.39, 73 ± 18		19.5	
73	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	57 ± 11		4.0-12.0	
74	[1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		4		
75	[1-(4-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		1.07	-20.8	
76	[1-(4-ethoxybenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	29.5	42.32, 42.22	-49.5	
77	[1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		7.89	32	
78	[1-(4-tert-butylbenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-14.4	
79	[1-(biphenyl-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
80	[1-(biphenyl-4-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-51.13	
81	[1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		-2.55	-0.6	
82	[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		20.23	-7.9	
83	[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		10.44	-48.6	
84	[3-(1,3-benzothiazol-2-ylmethyl)-1H-indol-1-yl]acetic acid			7.46	
85	[4-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		13.04	-25.1	
86	[4-chloro-1-(4-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid			-27.64	
87	[5-fluoro-1-(4-fluorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid		-8	-48.2	
88	[5-hydroxy-2-methyl-1-(3-methylbenzoyl)-1H-indol-3-yl]acetic acid		19.89	-27	
89	[5-hydroxy-2-methyl-1-(3-phenylprop-2-ynyl)-1H-indol-3-yl]acetic acid		3.38	6.1	
90	[5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid		18.34	23.5, 3.3	
91	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid		7.28	23.3	
92	[5-methoxy-1-(4-methoxybenzoyl)-2-methyl-1H-indol-3-yl]acetic acid	59	34.93, 6.4	-16.6	

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µM)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µM)
93	[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid		5.91, 25.18	-29.1	
94	[6-chloro-1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-19.7	
95	[6-chloro-1-(2,5-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-4.12	
96	[6-chloro-1-(2,6-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-35.53	
97	[6-chloro-1-(2-chloro-4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
98	[6-chloro-1-(2-chloro-6-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
99	[6-chloro-1-(2-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
100	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-9.1	
101	[6-chloro-1-(3-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid			-1.27	
102	[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid			8.94	
103	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-6.47	
104	[6-chloro-1-(3-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-6.24	
105	[6-chloro-1-(3-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-27	
106	[6-chloro-1-(4-chloro-2-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			0.49	
107	[6-chloro-1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	36 ± NA, 11 ± NA		-16.3	
108	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	66.71		-29	
109	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	32.26, 62.3 ± 32.5, 27 ± 13, 60 ± 16.5		-75.5 -46.84	
110	[6-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid			-10.37	
111	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	78 ± NA, 97 ± NA		50.19	10.4, 7.65
112	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		32	-61.6 -22.62	
113	[6-chloro-1-(4-chlorophenyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			10.99	
114	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		18.41 -16.38	-5.8	
115	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			11.7	

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µM)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µM)
116	[6-chloro-1-(cyclohexylmethyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				
117	[6-chloro-5-methoxy-1-(3-methoxybenzyl)-2-methyl-1H-indol-3-yl]acetic acid			-11.54	
118	[6-chloro-5-methoxy-2-methyl-1-(2-naphthylmethyl)-1H-indol-3-yl]acetic acid			-11.5	
119	[6-chloro-5-methoxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid			-23.87	
120	[6-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylmethyl)-1H-indol-3-yl]acetic acid			-79.1	
121	[6-chloro-5-methoxy-2-methyl-1-(quinolin-2-ylmethyl)-1H-indol-3-yl]acetic acid			-50.6	
122	[6-fluoro-1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		-6.87	1.7	
123	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		6.34	16.7	
124	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			18.17	
125	[6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid		7.62-8.22	42.6	27.73, 27.37
126	[6-fluoro-5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid			24.2	
127	[6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid		12.89	-4.7	
128	[6-fluoro-5-methoxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid			-9.7	
129	[1-(4-chlorophenyl)sulfonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		4.75	-38.6	
130	[1-(4-chlorophenyl)sulfonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			-19.7	
131	[1-(5-chloro-2-thienyl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		3.12	39.3	13.93
132	[1-(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		13.98	25.9	
133	[1-(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		8.11, 14.01	-15.2	
134	[1-(5-chloro-2-thienyl)methyl]-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		0	1.3	
135	[1-(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	125.0, 90.0	46.42	51.6	7.3, 4.95
136	[1-(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	51	28.98-6.47	2.3	
137	[1-(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		8.95	-1.4	
138	[1-(4-(difluoromethoxy)benzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		-2.6	-3.7	

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µM)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µM)
139	{1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		5.55	-56.8	
140	{1-[4-(difluoromethoxy)benzoyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	108 ± NA, 84 ± NA		0.3	
141	{1-[4-(difluoromethoxy)benzoyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	184.7, 135 ± NA, 157 ± NA		-13.4	
142	{5-fluoro-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		7	-35.5	
143	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		17.46	15.9	
144	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		4.8	48.4	4.77, 4.77
145	{5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl}acetic acid		21.06	-10.8	
146	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	179.2, 262 ± NA		-53.5	
147	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	44.5, 37.0	53.39	-21.9	
148	{6-chloro-1-[4-chlorophenoxy]carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid			-63.3	
149	{6-chloro-1-[5-chloro-2-thienyl]carbonyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid	28.0, 23.0	47.95	-25.6	
150	{6-chloro-1-[5-chloro-2-thienyl]carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid		19.16	32.6	
151	{6-chloro-1-[5-chloro-2-thienyl]carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		5.08	-1.8	
152	{6-chloro-1-[5-chloro-2-thienyl]methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		13.47	-1.4	
153	{6-chloro-1-[6-chloropyridin-3-yl]methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid			6.17 -37.93	
154	{6-chloro-1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	139.7, 99 ± NA, 118 ± NA		-73.3	
155	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid				
156	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethyl)benzoyl]-1H-indol-3-yl}acetic acid				
157	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid				
158	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		-0.94	20.2	
159	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		4.14	41.2	18.75, 18.75
160	{6-chloro-5-methoxy-1-[4-(methoxycarbonyl)benzoyl]-2-methyl-1H-indol-3-yl}acetic acid				
161	{6-chloro-5-methoxy-2-methyl-1-[(2-methyl-1,3-thiazol-4-yl)methyl]-1H-indol-3-yl}acetic acid			-14.81	

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µM)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µM)
162	(6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acetic acid			-10.21	
163	(6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid			2.04	
164	(6-chloro-5-methoxy-2-methyl-1-[4-(methylsulfonyl)benzyl]-1H-indol-3-yl)acetic acid			-10.69	
165	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid			-26.6	
166	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acetic acid		13.89	-17.4	
167	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid				
168	(6-fluoro-5-hydroxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl)acetic acid		2.81 -8.18	12	
169	(6-fluoro-5-hydroxy-2-methyl-1-[4-(methylthio)benzyl]-1H-indol-3-yl)acetic acid		-2.59	35.7	83.31
170	(6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acetic acid		18.83	24.4	
171	(6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid		18.58	-30.2	
172	(6-fluoro-5-methoxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl)acetic acid		17.12	-18.8	
173	(6-fluoro-5-methoxy-2-methyl-1-[4-(methylthio)benzyl]-1H-indol-3-yl)acetic acid		6.94	-12.4	
174	(6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acetic acid	89.14, 102 ± NA, 97 ± NA		-84.3	
175	(6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl)acetic acid	86.89, 117 ± NA		-50.9	
176	2-(trimethylsilyl)ethyl (6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetate			-25.8	
177	2-(trimethylsilyl)ethyl 1-[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate			-48.4	
178	2-(trimethylsilyl)ethyl 1-[1-(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate			-61.6	
179	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-piperidin-1-ylacetamide			-62.1	
180	2-[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetamide			-32.2	
181	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl 4-chlorobenzoate	132.4		-48.7	
182	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl acetate	0.97		-68.2	
183	3-[1-(1,3-benzothiazol-2-yl)methyl]-4,6-dichloro-2-methyl-1H-indol-3-ylpropanoic acid				
184	3-[1-(1,3-benzothiazol-2-yl)methyl]-6-chloro-2,5-dimethyl-1H-indol-3-ylpropanoic acid				

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µm)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µm)
185	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid				
186	3-[4,6-dichloro-1-(3-chlorobenzyl)-2-methyl-1H-indol-3-yl]propanoic acid				
187	3-[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid				
188	3-[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]propanoic acid			-29.07	
189	4-[(3-carboxymethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-1-ylmethyl]benzoic acid				
190	butyl 1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetate			-18.8	
191	ethyl 1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetate			-24.4	
192	indol-3-ylacetate	56.3, 18.5 ± 113, 19.9 ± 34		-38.2	
193	indol-3-ylacetate	76.79			
194	ethyl 1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-2-methyl-1H-indol-3-ylacetate	2 ± 1.85		-2.5	
195	ethyl N-[(1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetyl]amino butanoate	43.97, 46 ± 17		1.1	
196	ethyl N-[(1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetyl]glycinate		-5.48	-29.6	
197	isopropyl 1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetate			10.3	
198	methyl 1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetate				
199	methyl 1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetate	4.84, 1.6 ± 0.2		-8.3	
200	indol-3-ylacetate	0.66 ± 0.13		-25.2	
201	methyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-ylacetate	5.51, 5.4 ± 3, 12.6 ± 5.75, 4.2 ± 1.3		-12.8	
202	methyl N-[(1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetyl]-L-alanine			-6	
203	N-[(6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl]glycine		-18.7	-38.1	
204	propyl 1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-ylacetate			-26.2	
205	propyl 1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetate			-1.2	
206	propyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-ylacetate	36.46			
207	sec-butyl 1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-ylacetate			-0.4	

Row	IUPAC Name	FAAH Human Brain Homogenate Assay IC50 (µM)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10µM	DAO Assay Percent Inhibition at 10µM	DAO Assay IC50 (µM)
208	sec-butyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	88.6		-19.4 -2.7	
209	sec-butyl [6-chloro-1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetate			-28.5	

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
1	1-(1-(3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid (CRTH2 antagonist control)		0
2	1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid (COX and FAAH control)		
3	3-(3R)-3-[(4-fluorophenyl)sulfonylamino]-1,2,3,4-tetrahydro-8H-carbazol-9-yl)acetic acid (CRTH2 antagonist control)	0, 0, 2	29, 21
4	3'-(aminocarbonyl)biphenyl-3-yl cyclohexylcarbamate (FAAH control)		
5	4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (COX control)		
6	4-{4-(methylsulfonyl)phenyl}-3-phenylfuran-2(5H)-one (COX control)		
7	4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (COX control)		
8	5-benzoyl-2,3-dihydro-1H-pyrazoline-1-carboxylic acid (FAAH control)		
9	indole-2-carboxylic acid (DAO control)		
10	[5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid		
11	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid		
12	(1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
13	(1-benzyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0, 0	20
14	(5-fluoro-2-methyl-1H-indol-3-yl)acetic acid		
15	[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	9, 56
16	[1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	13, 85
17	[1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
18	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
19	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
20	[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	0
21	[1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
22	[1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	19, 5
23	[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
24	(1-[(4-chlorophenyl)sulfonyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0, 0	27.53
25	(1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		1
26	(1-[(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
27	(5-hydroxy-2-methyl-1-[(2E)-3-phenylprop-2-en-1-yl]-1H-indol-3-yl)acetic acid	0, 0	11.93
28	(5-methoxy-2-methyl-1-[(2E)-3-phenylprop-2-en-1-yl]-1H-indol-3-yl)acetic acid	0.5	0
29	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-hydroxyethyl)acetamide		
30	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-phenylethyl)acetamide		
31	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethanol		
32	ethyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
33	ethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
34	ethyl N-[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate]		
35	N-[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl]glycine		
36	[(6-fluoro-5-hydroxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl)acetic acid]	0	
37	[(6-fluoro-5-methoxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl)acetic acid]		
38	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0	
39	(1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0	0
40	(1-benzoyl-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	0, 0	7.54
41	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0	39.59
42	(6-chloro-1-[(4-chlorophenyl)amino]carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
43	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid		
44	(6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid		
45	(6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid	0, 3.2	10.97
46	(6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid		

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
47	(6-fluoro-5-methoxy-2-methyl-1-(4-((trifluoromethyl)thio)benzyl)-1H-indol-3-yl)acetic acid		
48	(1-(1,3-benzothiazol-2-ylmethyl)-4-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
49	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl)acetic acid	0	19.5
50	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid		
51	(1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	1.6	0
52	(1-(1,3-benzothiazol-2-ylmethyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
53	(1-(1,3-benzoxazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
54	(1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0	14.2
55	(1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0	20.5
56	(1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0, 0	11.99
57	(1-(2-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
58	(1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0, 0	0
59	(1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0	0
60	(1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0	14.6
61	(1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0, 0	8.5
62	(1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0	20.33
63	(1-(4-bromobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid		
64	(1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
65	(1-(4-bromobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0, 0	18.84
66	(1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		
67	(1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid		
68	(1-(4-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0, 0	0
69	(1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
70	[1-(4-chlorobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
71	[1-(4-chlorobenzoyl)-4-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
72	[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
73	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
74	[1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	0, 0.2	6.44
75	[1-(4-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	
76	[1-(4-ethylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
77	[1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
78	[1-(4-tert-butylbenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
79	[1-(biphenyl-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
80	[1-(biphenyl-4-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
81	[1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
82	[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
83	[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	0
84	[3-(1,3-benzothiazol-2-ylmethyl)-1H-indol-1-yl]acetic acid		
85	[4-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
86	[4-chloro-1-(4-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		
87	[5-fluoro-1-(4-fluorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid	0, 0.7	0
88	[5-hydroxy-2-methyl-1-(3-methylbenzoyl)-1H-indol-3-yl]acetic acid		
89	[5-hydroxy-2-methyl-1-(3-phenylprop-2-ynoyl)-1H-indol-3-yl]acetic acid	0, 0	15.1
90	[5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid		
91	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	0	
92	[5-methoxy-1-(4-methoxybenzoyl)-2-methyl-1H-indol-3-yl]acetic acid	0	

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
93	[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	0	
94	[6-chloro-1-(2,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
95	[6-chloro-1-(2,5-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
96	[6-chloro-1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
97	[6-chloro-1-(2-chloro-4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
98	[6-chloro-1-(2-chloro-6-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
99	[6-chloro-1-(2-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	6.6, 0	48.3
100	[6-chloro-1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
101	[6-chloro-1-(3-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	0	23.4
102	[6-chloro-1-(3-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	0	
103	[6-chloro-1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0.1, 0	54.74
104	[6-chloro-1-(3-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	
105	[6-chloro-1-(3-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
106	[6-chloro-1-(4-chloro-2-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
107	[6-chloro-1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		
108	[6-chloro-1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
109	[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
110	[6-chloro-1-(4-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	2.8	19.74
111	[6-chloro-1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
112	[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	0
113	[6-chloro-1-(4-chlorophenyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
114	[6-chloro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
115	[6-chloro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
116	[6-chloro-1-(cyclohexylmethyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
117	[6-chloro-5-methoxy-1-(3-methoxybenzyl)-2-methyl-1H-indol-3-yl]acetic acid		
118	[6-chloro-5-methoxy-2-methyl-1-(2-naphthylmethyl)-1H-indol-3-yl]acetic acid		
119	[6-chloro-5-methoxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid	0	
120	[6-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylmethyl)-1H-indol-3-yl]acetic acid		
121	[6-chloro-5-methoxy-2-methyl-1-(quinolin-2-ylmethyl)-1H-indol-3-yl]acetic acid		
122	[6-fluoro-1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
123	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
124	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
125	[6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	0	0
126	[6-fluoro-5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid		
127	[6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	0	5.5
128	[6-fluoro-5-methoxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid		
129	[1-[(4-chlorophenyl)sulfonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	0
130	[1-[(4-chlorophenyl)sulfonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
131	[1-[(5-chloro-2-thienyl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0	0
132	[1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0	
133	[1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		
134	[1-[(5-chloro-2-thienyl)methyl]-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		19.24
135	[1-[(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0	0
136	[1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	26.3
137	[1-[(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		
138	[1-[(4-(difluoromethoxy)benzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
139	{1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		
140	{1-[4-(difluoromethoxy)benzoyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid		
141	{1-[4-(difluoromethoxy)benzoyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		
142	{5-fluoro-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	0, 8.8	0
143	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		
144	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		7.7
145	{5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl}acetic acid		
146	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		
147	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	0	10.5
148	{6-chloro-1-[4-(chlorophenoxy)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		
149	{6-chloro-1-[5-chloro-2-thienylcarbonyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid		
150	{6-chloro-1-[5-chloro-2-thienylcarbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid		
151	{6-chloro-1-[5-chloro-2-thienylcarbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	0	
152	{6-chloro-1-[5-chloro-2-thienylmethyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	25	
153	{6-chloro-1-[6-chloropyridin-3-ylmethyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		
154	{6-chloro-1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		
155	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		
156	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethyl)benzoyl]-1H-indol-3-yl}acetic acid		
157	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		
158	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid		
159	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	0	0
160	{6-chloro-5-methoxy-1-[4-(methoxycarbonyl)benzoyl]-2-methyl-1H-indol-3-yl}acetic acid		
161	{6-chloro-5-methoxy-2-methyl-1-[2-methyl-1,3-thiazol-4-ylmethyl]-1H-indol-3-yl}acetic acid		

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
162	[6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl]acetic acid	0	27.5
163	[6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl]acetic acid	0	17.2
164	[6-chloro-5-methoxy-2-methyl-1-[4-(methylsulfonyl)benzyl]-1H-indol-3-yl]acetic acid		
165	[6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid		
166	[6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl]acetic acid	0	19
167	[6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl]acetic acid		
168	[6-fluoro-5-hydroxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl]acetic acid	0	0
169	[6-fluoro-5-hydroxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl]acetic acid		
170	[6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid		
171	[6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid		
172	[6-fluoro-5-methoxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl]acetic acid	0	
173	[6-fluoro-5-methoxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl]acetic acid		
174	[6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid		
175	[6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid		
176	2-(trimethylsilyl)ethyl (6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetate		
177	2-(trimethylsilyl)ethyl [1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
178	2-(trimethylsilyl)ethyl {1-[(6-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetate		
179	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-piperidin-1-ylacetamide		
180	2-[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetamide		
181	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl 4-chlorobenzoate		
182	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl acetate		
183	3-[1-(1,3-benzothiazol-2-yl)methyl]-4,6-dichloro-2-methyl-1H-indol-3-ylpropanoic acid		
184	3-[1-(1,3-benzothiazol-2-yl)methyl]-6-chloro-2,5-dimethyl-1H-indol-3-ylpropanoic acid		

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
185	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid		
186	3-[4,6-dichloro-1-(3-chlorobenzoyl)-2-methyl-1H-indol-3-yl]propanoic acid		
187	3-[6-chloro-1-(3-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid		
188	3-[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]propanoic acid	0	0
189	4-[(3-carboxymethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-1-ylmethyl]benzoic acid		
190	butyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
191	ethyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
192	ethyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
193	ethyl [6-chloro-1-(4-(difluoromethoxy)benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
194	ethyl 4-[(1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)amino]butanoate		
195	ethyl N-[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
196	ethyl N-[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
197	isopropyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
198	methyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
199	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
200	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
201	methyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
202	methyl N-[(1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)amino]acetate		
203	N-[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
204	propyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
205	propyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		
206	propyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
207	sec-butyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		

Row	IUPAC Name	DP-1 Agonist Assay- % of maximal response	DP-1 Antagonist Assay- % of maximal response
208	sec-butyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		
209	sec-butyl [6-chloro-1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetate		

FIGURE 4

Row	IUPAC Name	DAO Activity Percent Inhibition at 10 μ M	DAO IC50 (μ m)
1	1H-indole-2-carboxylic acid (positive control)	96	0.71, 0.62, 0.49
2	(1-methyl-1H-indol-3-yl)(oxo)acetic acid	-36.3	
3	(2E)-3-(1H-indol-3-yl)acrylic acid	6.4	
4	(3S)-2,3,4,9-tetrahydro-1H-b-carboline-3-carboxylic acid	-2.96	
5	(5-bromo-1H-indol-3-yl)acetic acid	4.1	
6	(5-methoxy-1H-indol-3-yl)acetic acid	-40.2	
7	1-(phenylsulfonyl)-1H-indole-3-carbaldehyde	-2.2	
8	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride	-12.17	
9	1H-benzimidazole-2-sulfonic acid	-48.7, 15.25	
10	1H-indole-3-carboxylic acid	-13.2	
11	1H-indole-5-carboxylic acid	-9.7	
12	1H-indole-6-carboxylic acid	-6.7	
13	1H-pyrrole-2-carboxylic acid	71.09	1.26, 1.26
14	1-methyl-1H-indole-2-carboxylic acid	-2.3	
15	2-hydroxy-3-(1H-indol-3-yl)propanoic acid	-6.62	
16	2'-hydroxy-3-methylisovaline	-42.21	
17	3-(1H-benzimidazol-2-yl)propanoic acid	-12.21	
18	5-chloro-1H-indole-2-carboxylic acid	66.6, 54.54, 74.28	5.6, 5.6
19	5-fluoro-1H-indole-2-carboxylic acid	93.5, 72.9	0.38 0.38
20	5-hydroxy-1H-indole-2-carboxylic acid	60.5	1.07, 1.07
21	5-hydroxy-1H-indole-3-carboxylic acid	58.7	4.5, 0.93
22	5-methoxy-1H-indole-2-carboxylic acid	11.5	
23	5-phenyl-2-furoic acid	-8.71	
24	α -(hydroxymethyl)-D-tyrosine	-12.18	
25	α -(hydroxymethyl)phenylalanine	-17.2	
26	ethyl 2-methyl-1H-indole-3-carboxylate	-6.8	
27	indoline-2-carboxylic acid	37.34	2.87, 2.87
28	methyl 1H-indole-3-carboxylate	-2.3	
29	methyl 4,6-dimethoxy-1H-indole-2-carboxylate	0.1	
30	methyl 4-methoxy-1H-indole-2-carboxylate	-6	
31	methyl 6-methoxy-1H-indole-2-carboxylate	-8.2	
32	piperidine-2-carboxylic acid	-13.3	
33	proline	-16.17	
34	pyridine-2-carboxylic acid	-6.48	

FIGURE 5

Row	IUPAC Name	COX-1 Purified Enzyme Assay IC50 (μm)	COX-2 Purified Enzyme Assay IC50 (μm)	FAAH Human Brain Homogenate Assay Percent Inhibition at 10μM	CD11B Antagonist Assay IC60 (nM)	DAO Assay Percent Inhibition at 10μM
1	[1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl](oxo)acetic acid	>100	>100		>1μM	
2	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	>100	>100	7.8	3.4	
3	[6-chloro-1-(2,3-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		37	
4	[6-chloro-1-(3,5-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		4	
5	[5-fluoro-1-(3-(trifluoromethoxy)benzyl)-1H-indol-2-yl](oxo)acetic acid	>100	>100		1076	
6	[5-fluoro-2-methyl-1-(3-(trifluoromethoxy)benzyl)-1H-indol-3-yl](oxo)acetic acid				434	
7	[6-chloro-2,5-dimethyl-1-(3-(trifluoromethoxy)benzyl)-1H-indol-3-yl]acetic acid	>100	>100, >100	10.9	2.4, 3.0	2.2
8	[6-chloro-2,5-dimethyl-1-(3-(trifluoromethyl)benzyl)-1H-indol-3-yl]acetic acid	>100	>100	14.3	8	9.1
9	[6-chloro-5-fluoro-2-methyl-1-(3-(trifluoromethoxy)benzyl)-1H-indol-3-yl]acetic acid	>10, 100	>100, >100	-0.6	3.5	
10	[6-chloro-5-fluoro-2-methyl-1-(3-(trifluoromethyl)benzyl)-1H-indol-3-yl]acetic acid	100	>100		10	
11	[6-fluoro-2,5-dimethyl-1-(3-(trifluoromethoxy)benzyl)-1H-indol-3-yl]acetic acid		>100		<0.1	
12	[6-fluoro-5-methoxy-2-methyl-1-(3-(trifluoromethyl)benzyl)-1H-indol-3-yl]acetic acid	>100	>100		12	
13	1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indole-3-carboxylic acid	>100	>100	31.5	>1μM	
14	3-[1-(1,3-benzothiazol-2-ylmethyl)-4,6-dichloro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100	2.8	29	-8
15	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl]propanoic acid	>100	>100	-1.4	249	-0.9
16	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100	14.6	194	9.6
17	3-[4,6-dichloro-1-(3-chlorobenzyl)-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100	16.1	57	5.1
18	3-[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100	11.9	39	14.8

FIGURE 6

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
1	control-celebrex	15, 12	0.22, 0.17	12.08±0.75 (n=5)	0.42±0.02 (n=5)
2	control-rofecoxib	>100	3.2	39	0.24
3	control-valdecoxib	>100	0.04	100	0.15
4	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	3	0.3		
5	(1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0.3	0.22		
6	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	0.33, 0.26		
7	(1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	10.5	0.35		
8	(1-benzoyl-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
9	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>10		
10	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
11	(2E)-3-{5-chloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acrylic acid	>100	>100		
12	(2E)-3-{5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acrylic acid		>100		
13	(2E)-3-{5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acrylic acid	>100	>100		
14	(5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	>100	>100		
15	(6-chloro-5-methoxy-2-methyl-1-{4-[(trifluoromethyl)thio]benzoyl}-1H-indol-3-yl)acetic acid	>100	>100		
16	(6-chloro-5-methoxy-2-methyl-1-{4-[(trifluoromethyl)thio]benzyl}-1H-indol-3-yl)acetic acid	>100	>100		
17	(6-fluoro-5-hydroxy-2-methyl-1-{4-[(trifluoromethyl)thio]benzoyl}-1H-indol-3-yl)acetic acid	>100, >10	>10, >100		
18	(6-fluoro-5-methoxy-2-methyl-1-{4-[(trifluoromethyl)thio]benzoyl}-1H-indol-3-yl)acetic acid	>10	>10		
19	(6-fluoro-5-methoxy-2-methyl-1-{4-[(trifluoromethyl)thio]benzyl}-1H-indol-3-yl)acetic acid	100	>100		
20	[1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl]oxoacetic acid	>100	>100		
21	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl]acetic acid	>100	>100		
22	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
23	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100, >10, >100	>10, >10, >100		
24	[1-(1,3-benzothiazol-2-ylmethyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>10, >100	>100, >10		
25	[1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
26	[1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
27	[1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	29.9 ND	>10		
28	[1-(2-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100			>100
29	[1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
30	[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
31	[1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
32	[1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
33	[1-(3-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>10	>100, >100		
34	[1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
35	[1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
36	[1-(4-bromobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	21.1, 26.3	0.18, 0.16	60.9	0.67
37	[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	2.2	0.14		
38	[1-(4-bromobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
39	[1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	24.6	>10		
40	[1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
41	[1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	20.4	7.1		
42	[1-(4-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	10	>100		
43	[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	<10			<10
44	[1-(4-chlorobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
45	[1-(4-chlorobenzoyl)-4-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100, >100	1.3, 4.3	59.7	8
46	[1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	50	4		
47	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	9.3±0.87 (n=6)	.19±0.04 (n=6)	12.9	0.51
48	[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	30.1±3.3 (n=5)	0.33±0.02 (n=5)	30.2, 28.8	0.60, 0.79
49	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	5, 2.3	1.5, 0.6		
50	[1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
51	[1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	60	>10		
52	[1-(4-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	72	2.7		
53	[1-(4-ethylbenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0.2	>10		
54	[1-(4-fluorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	14	0.9		
55	[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0.6	0.4		
56	[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10		
57	[1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	3.03		
58	[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	3.22		
59	[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	0.8		
60	[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	0.4		
61	[4-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>30		
62	[4-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	10	>100		>100
63	[5-fluoro-1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
64	[5-hydroxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid	>100	>10		
65	[5-hydroxy-2-methyl-1-(3-phenylprop-2-ynyl)-1H-indol-3-yl]acetic acid	4.9	>10		
66	[5-hydroxy-2-methyl-1-(4-methylbenzyl)-1H-indol-3-yl]acetic acid	0.45	0.3		
67	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	>100	8.9		
68	[5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]acetic acid	31.9	>100		
69	[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	>100	>22.2		
70	[6-chloro-1-(2,3-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
71	[6-chloro-1-(2-chloro-4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>10, >100	>10, >100		
72	[6-chloro-1-(2-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	100	>100		
73	[6-chloro-1-(3,5-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		>100		
74	[6-chloro-1-(3,5-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
75	[6-chloro-1-(3,5-difluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	100	>100		

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
76	[6-chloro-1-(3,5-dimethylbenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>10, >10, 10	>100, >100, >100		
77	[6-chloro-1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
78	[6-chloro-1-(3-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	>10, 4.7	>100, >100		
79	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	10, 72.0	>10, >100		
80	[6-chloro-1-(3-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
81	[6-chloro-1-(3-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>10	>100		
82	[6-chloro-1-(4-chloro-2-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
83	[6-chloro-1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	100, >100	>10, >100	>100	>100
84	[6-chloro-1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	1.7		
85	[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	31.78±11.30 (n=11)	1.16±1.67 (n=11)	14	0.43
86	[6-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	>10	>100		>100
87	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	16.1, >100, 30.4, <10	>10, >100		
88	[6-chloro-1-(4-chlorophenyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100			>100
89	[6-chloro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	0.21, 0.37		
90	[6-chloro-1-(cyclohexylmethyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100		
91	[6-chloro-5-methoxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid	>10	>100		
92	[6-chloro-5-methoxy-2-methyl-1-(3-nitrobenzyl)-1H-indol-3-yl]acetic acid	>10, >100	>100, >100		
93	[6-chloro-5-methoxy-2-methyl-1-(quinolin-2-ylmethyl)-1H-indol-3-yl]acetic acid	>10, >100	>100, >10		
94	[6-fluoro-1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	0.18	26.6	0.63
95	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	8.2	0.13	3.1	0.36
96	[6-fluoro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>10			>100
97	[6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	27.3	0.23	14.5	0.2
98	[6-fluoro-5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid	3.6	0.27		
99	[6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	6.3	0.32		
100	[6-fluoro-5-methoxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid	1	0.13		

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
101	{1-[(4-chlorophenyl)sulfonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>10		
102	{1-[(4-chlorophenyl)sulfonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100, >100	>10, >10		
103	{1-[(4-chlorophenyl)sulfonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100, >10	>100, >100		
104	{1-[(5-chloro-2-thienyl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	5.5	0.5		
105	{1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	5	0.2		
106	{1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	85, 90	0.56, 0.6	36	0.86
107	{1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	35	0.2	7.1	0.48
108	{1-[(5-chloro-2-thienyl)methyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid	>100	>10		
109	{1-[(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>100		
110	{1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>100		
111	{1-[(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>10		
112	{1-[(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	2.8		
113	{1-[3,5-bis(trifluoromethyl)benzyl]-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	100	>100		
114	{1-[4-(difluoromethoxy)benzoyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	45	0.25	67.43	0.63
115	{1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	4.9	0.56		
116	{1-[4-(difluoromethoxy)benzoyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	0.2	71	0.85
117	{1-[4-(difluoromethoxy)benzoyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	18.1	0.1	12.2	0.19
118	{2-chloro-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
119	{2-chloro-3-[3-(trifluoromethoxy)benzyl]-1H-indol-1-yl}acetic acid	>100	>100		
120	{2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
121	{2-oxo-1-[3-(trifluoromethoxy)benzyl]-2,3-dihydro-1H-indol-3-yl}acetic acid	>100	>100		
122	{4,6-dichloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
123	{5,6-dichloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	100, 100, 23	>100, >100, 100		
124	{5-chloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
125	{5-chloro-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	100	>100		

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
126	{5-fluoro-1-[3-(trifluoromethoxy)benzyl]-1H-indol-2-yl}(oxo)acetic acid	>100	>100		
127	{5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
128	{5-fluoro-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>10		
129	{5-hydroxy-2-methyl-1-[(2E)-3-phenylprop-2-enoyl]-1H-indol-3-yl}acetic acid	0.1	>8		
130	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	>100	40		
131	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
132	{5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl}acetic acid	25	>100		
133	{5-methoxy-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
134	{5-methoxy-2-methyl-1-[(2E)-3-phenylprop-2-enoyl]-1H-indol-3-yl}acetic acid	0.1	5.45		
135	{5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		>100		
136	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	>100	0.2	21.5	0.6
137	{5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
138	{5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl}acetic acid	16.8	0.4		
139	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid	>10	>10		
140	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>10	>10		
141	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100, 71.3	>10, >100		
142	{6-chloro-1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>10		
143	{6-chloro-1-[(6-chloropyridin-3-yl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>10	>100		
144	{6-chloro-1-[3-(difluoromethoxy)benzyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>100		
145	{6-chloro-1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100, >100	0.28, 0.67	54.33	0.66
146	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100, >100		
147	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
148	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>10, 100	>100, >100		
149	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	100	>100		
150	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	>100	>100		

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
151	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
152	{6-chloro-5-methoxy-1-[4-(methoxycarbonyl)benzyl]-2-methyl-1H-indol-3-yl}acetic acid	>100	>100		
153	{6-chloro-5-methoxy-2-methyl-1-[(2-methyl-1,3-thiazol-4-yl)methyl]-1H-indol-3-yl}acetic acid	>100			>100
154	{6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
155	{6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	>10, 12.8, 4.5	>100, >100		
156	{6-chloro-5-methoxy-2-methyl-1-[4-(methylsulfonyl)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
157	{6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	>100	>100	>100	>100
158	{6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	24.9, >10	>100, >100		>100
159	{6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	>10	>10		
160	{6-fluoro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	100, 100	>100, >100, >100		
161	{6-fluoro-5-hydroxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl}acetic acid	16.3	0.41		
162	{6-fluoro-5-hydroxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl}acetic acid	>100	>10		
163	{6-fluoro-5-hydroxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl}acetic acid	0.3	0.36		
164	{6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	>100	>8		
165	{6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl}acetic acid	>100	>8		
166	{6-fluoro-5-methoxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl}acetic acid	3.3	0.29		
167	{6-fluoro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	>100	>100		
168	{6-fluoro-5-methoxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl}acetic acid	>100	>10		
169	{6-fluoro-5-methoxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl}acetic acid	0.2	0.06		
170	{6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl}acetic acid	>100, >100, >100	0.4, 0.59, 0.31	41.8	0.35
171	{6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl}acetic acid	95, 76.2	0.45, 0.37	27.2	0.6
172	1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indole-3-carboxylic acid	>100	>100		
173	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-hydroxyethyl)acetamide	>100	>10		
174	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-phenylethyl)acetamide			>100	>100
175	2-[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetamide	>100	>10		

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
176	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethanol	>100	4.81	90.93	1.8
177	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl 4-chlorobenzoate	>100	>10		
178	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl acetate	>100	>10		
179	3-[1-(1,3-benzothiazol-2-ylmethyl)-4,6-dichloro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		
180	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl]propanoic acid	>100	>100		
181	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		
182	3-[4,6-dichloro-1-(3-chlorobenzyl)-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		
183	3-[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		
184	3-[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]propanoic acid	>100	>100		>100
185	4-[[3-(carboxymethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-1-yl]methyl]benzoic acid	<10	>10		
186	5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indole-3-carbaldehyde		>100		
187	6-chloro-2,3-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indole acetate	>100	>100		
188	butyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	21.3	7.98		
189	control-indomethacin	.13±.04 (n=5)	.51±.54 (n=5)	0.14, 0.14, 0.22, 0.22	0.25, 0.25, 0.2, 0.2
190	ethyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	12.9	11.48		
191	ethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	36.9, >100	>50, >50		
192	ethyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	33	5.98		
193	ethyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10	>100	>100
194	ethyl [6-chloro-1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
195	ethyl 4-[[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetyl]amino]butanoate	>100	>50		
196	ethyl N-[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl]glycinate	8.6	>10		
197	ethyl N-[[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetyl]glycinate	>100	>10		
198	ethyl N-[[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl]glycinate			>100	>100
199	isopropyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	11	0.66		
200	methyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	15, 16	>10, >100		

Row	Compound	COX-1 enzyme IC50 (uM)	COX-2 enzyme IC50 (uM)	Human whole blood COX-1 IC50 (uM)	Human whole blood COX-2 IC50 (uM)
201	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	45.1, 30.1	18.53, 8.38		
202	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
203	methyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100, >100	>10, >100		
204	methyl N-[[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetyl]-L-alaninate	>100	>10		
205	N-[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl]glycine			61.6	>100
206	N-[[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl]glycine	>100	>100		
207	propyl (5-hydroxy-2-methyl-1H-indol-3-yl)acetate	>100	>50		
208	propyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	5.3	8.41		
209	propyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	28	5.79		
210	propyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
211	sec-butyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	>100	>50		
212	sec-butyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
213	sec-butyl [6-chloro-1-(4-(difluoromethoxy)benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	>100	>10		
214	tert-butyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate			>100	>100

FIGURE 7

Row	Compound	Agonist EC50 (nM) CD11b	CD11b agonist activity at 10 nM	CD11B Antagonist Activity IC50 (nM) In 10 Percent Human Plasma	CD11B Antagonist Activity IC50 (nM) CD11b	CD11b Antagonist Activity at 10uM
1	control - Ramatroban (3-(3R)-3-((4-fluorophenyl)amino)-1,2,3,4-tetrahydro-9H-carbazol-9-yl)propanoic acid)		-12.5	690±334 (n=8)	30±17 (n=26)	87
2	control known CRTH2 antagonist ([1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid)		0	322	10	
3	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		29.1			46.8
4	(1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid					60.4
5	(1-benzyl-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid		6, -9.5		166, 126	91.2
6	(1-benzyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	>100,000	-9.5		1007	92.4
7	(1-benzyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		0	7000	20, 21.4	
8	(2E)-3-(5-chloro-2-methyl-1-{3-(trifluoromethoxy)benzyl}-1H-indol-3-yl)acrylic acid			>1uM	21	
9	(2E)-3-(5-fluoro-2-methyl-1-{3-(trifluoromethoxy)benzyl}-1H-indol-3-yl)acrylic acid		4	4200	37	
10	(2E)-3-(5-methoxy-2-methyl-1-{3-(trifluoromethoxy)benzyl}-1H-indol-3-yl)acrylic acid			>1uM	11, 47	
11	(6-chloro-1-(((4-chlorophenyl)amino)carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid		0		114	
12	(6-chloro-5-methoxy-2-methyl-1-(4-((trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid				2300	
13	(6-chloro-5-methoxy-2-methyl-1-(4-((trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid		6.84		84	
14	(6-fluoro-5-hydroxy-2-methyl-1-(4-((trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid		-10.5	634	23.8±18.8 (n=7)	99.8
15	(6-fluoro-5-methoxy-2-methyl-1-(4-((trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid		13.68		98	
16	(6-fluoro-5-methoxy-2-methyl-1-(4-((trifluoromethyl)thio)benzoyl)-1H-indol-3-yl)acetic acid		0		286	
17	[1-(1,3-benzothiazol-2-ylmethyl)-4-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		734	
18	[1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl]oxoacetic acid		0		>1uM	
19	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl]acetic acid		3.7	1504	2, 6, 3	
20	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		0	814	3.4, 3	
21	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0	4921	22.6±10.4 (n=11)	
22	[1-(1,3-benzothiazol-2-ylmethyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		98	
23	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		151	
24	[1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid					75.2
25	[1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid					60.4
26	[1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		9		177	91.2
27	[1-(2-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		1.2		187	
28	[1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		-1.2, -9.5		181, 120.4	104.7
29	[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		2.8, -2.6		226, 203.3	96.1
30	[1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		-0.3		151.9	89.9
31	[1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid					78.9
32	[1-(3-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		14.3, 17.4		7.0, 4.0	
33	[1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		-2.3		647	91.2
34	[1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100,000			114	82.5
35	[1-(4-bromobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	26				

Row	Compound	Agonist EC50 (nM) CD11b	CD11b agonist activity at 10 uM	CD11b Antagonist Activity IC50 (nM) in 10 Percent Human Plasma	CD11b Antagonist Activity IC50 (nM) CD11b	CD11b Antagonist Activity at 10uM
36	[1-(4-bromobenzyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		0.8	>10 uM	109, 47	92.4
37	[1-(4-bromobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		-7.4		396, 408.1	101
38	[1-(4-bromobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				234	96.1
39	[1-(4-bromobenzyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		100	
40	[1-(4-bromobenzyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		50	
41	[1-(4-chlorobenzyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		104.1			
42	[1-(4-chlorobenzyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		91.5			
43	[1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		4.9, -0.3		113, 530	96.1
44	[1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 100 uM				
45	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				103.8	99.8
46	[1-(4-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid					48
47	[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid					77.6
48	[1-(4-tert-butylbenzyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		38.2		364	
49	[1-(biphenyl-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		16.24			
50	[1-(biphenyl-4-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		126, 205	
51	[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0.9			51.7
52	[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				171	91.2
53	[3-(1,3-benzothiazol-2-ylmethyl)-1H-indol-1-yl]acetic acid		0			
54	[4-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 10 uM	55.3			
55	[4-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		0		78	
56	[5-fluoro-1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]acetic acid		1.9, -28.9	>10 uM	>100, 23.02	98.6
57	[5-hydroxy-2-methyl-1-(3-phenylprop-2-ynyl)-1H-indol-3-yl]acetic acid				806.8	102.3
58	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid		0.4			46.8
59	[5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 100 uM	3.2			39.4
60	[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid		0.4			6.2
61	[6-chloro-1-(2,3-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0	>10 uM	37, 53	
62	[6-chloro-1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		3.42		95	
63	[6-chloro-1-(2,5-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		27.35		20, 40	
64	[6-chloro-1-(2,6-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0.85		468, 722, 126	
65	[6-chloro-1-(2-chloro-4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		2.15		80, 499	
66	[6-chloro-1-(2-chloro-6-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		97, 171	
67	[6-chloro-1-(2-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0	>10 uM	48, 38, 16.9	
68	[6-chloro-1-(3,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		91	
69	[6-chloro-1-(3,4-difluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		1.71		129	
70	[6-chloro-1-(3,5-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		12.7, 1.3	5000	27, 19	

Row	Compound	Agonist EC50 (nM) CD11b	CD11b agonist activity at 10 uM	CD11B Antagonist Activity IC50 (nM) in 10 Percent Human Plasma	CD11B Antagonist Activity IC50 (nM) CD11b	CD11b Antagonist Activity at 10uM
71	[6-chloro-1-(3,5-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0	7000, 1100	4, 8	
72	[6-chloro-1-(3,5-difluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				50	
73	[6-chloro-1-(3,5-dimethylbenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid			3000, 5000	3, 13, 5, 10	
74	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		4.27		555	
75	[6-chloro-1-(3-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		18.3	2736	9, 13, 11	
76	[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		9.2	4000	26, 39	
77	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		2.05	3019	15.3±9.83 (n=6)	
78	[6-chloro-1-(3-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		7.4	2000	26, 47	
79	[6-chloro-1-(3-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		13.7	6000	32, 72.5	
80	[6-chloro-1-(4-chloro-2-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		15.2		94	
81	[6-chloro-1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	20				
82	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	66				
83	[6-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid		0	>10 uM	16, 31, 32, 33	
84	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		0	>10 uM	75, 37	
85	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0, 6.3, -4.3	56070	94, 32.7, 40, 43	94.9
86	[6-chloro-1-(4-chlorophenyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		52.2	>10 uM	29	
87	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		35.3			
88	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		52	
89	[6-chloro-1-(cyclohexylmethyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		106	
90	[6-chloro-5-methoxy-1-(3-methoxybenzyl)-2-methyl-1H-indol-3-yl]acetic acid		0		53.4	
91	[6-chloro-5-methoxy-2-methyl-1-(2-naphthylmethyl)-1H-indol-3-yl]acetic acid		23.08			
92	[6-chloro-5-methoxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid		9.2	3000	16, 37	
93	[6-chloro-5-methoxy-2-methyl-1-(3-nitrobenzyl)-1H-indol-3-yl]acetic acid				23	
94	[6-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylmethyl)-1H-indol-3-yl]acetic acid		117.09		561	
95	[6-chloro-5-methoxy-2-methyl-1-(quinolin-2-ylmethyl)-1H-indol-3-yl]acetic acid		0		63, 212	
96	[6-fluoro-1-(4-fluorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	partial agonist at 10 uM				
97	[6-fluoro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		4.4		238	
98	[6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	>100,000	2.1			54.2
99	[6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid		-0.4			73.9
100	[1-[(4-chlorophenyl)sulfonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		-9.5		384, 203	103.5
101	[1-[(4-chlorophenyl)sulfonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		-5.4		2135, 71	103.5
102	[1-[(4-chlorophenyl)sulfonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		278	
103	[1-[(5-chloro-2-thienyl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		0.4		173	86.2
104	[1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		-0.4	>10 uM	11	87.5
105	[1-[(3-chloro-2-thienyl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100,000	0		86	

Row	Compound	Agonist EC 50 (nM) CD11b	CD11b agonist activity at 10 uM	CD11b Antagonist Activity IC50 (nM) in 10 Percent Human Plasma	CD11b Antagonist Activity IC50 (nM) CD11b	CD11b Antagonist Activity at 10uM
106	{1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		23.2			57.9
107	{1-[(5-chloro-2-thienyl)methyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid		14.1, -1.3		61.9	86.2
108	{1-[(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	partial agonist at 100 uM	10.5, 4.9		172.1	86.2
109	{1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100,000	13.9			80.1
110	{1-[3,5-bis(trifluoromethyl)benzyl]-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid			9000	27, 41, 18	
111	{1-[4-(difluoromethoxy)benzyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	partial agonist at 10 nM				
112	{1-[4-(difluoromethoxy)benzyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	787				
113	{1-[4-(difluoromethoxy)benzyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	450				
114	{2-chloro-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid			3000	30	
115	{2-chloro-3-[3-(trifluoromethoxy)benzyl]-1H-indol-1-yl}acetic acid				31, 16	
116	{2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				12, 14	
117	{2-oxo-1-[3-(trifluoromethoxy)benzyl]-2,3-dihydro-1H-indol-3-yl}acetic acid			>10 uM	3400	
118	{3-[[4-(4-fluorophenyl)butyl]amino]-1,2,3,4-tetrahydro-9H-carbazol-9-yl}acetic acid		0, 0	0.15	0.07	
119	{4,6-dichloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		0	757	3	
120	{5,6-dichloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid			1300, 820	2, 2, 4	
121	{5-chloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid			851	9, 18	
122	{5-chloro-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid				27	
123	{5-fluoro-1-[3-(trifluoromethoxy)benzyl]-1H-indol-2-yl}(oxo)acetic acid		0		1076, 864	
124	{5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}(oxo)acetic acid		0		434	
125	{5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				33	
126	{5-fluoro-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		0.5, -0.3	>10 uM	142, 49	94.9
127	{5-hydroxy-2-methyl-1-[(2E)-3-phenylprop-2-en-1-yl]-1H-indol-3-yl}acetic acid				105.1	98.6
128	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		35.9			
129	{5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid		43.8			
130	{5-methoxy-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				112, 79, 73	
131	{5-methoxy-2-methyl-1-[(2E)-3-phenylprop-2-en-1-yl]-1H-indol-3-yl}acetic acid			>10 uM	26.9	83.8
132	{5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		0	2100	23	
133	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	>1000				
134	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	partial agonist at 100 uM	3.9			80.1
135	{5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid		48.6			
136	{6-chloro-1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		24.79		>10000	
137	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid		2.56		95	
138	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid		44.44		1948	
139	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		34.2, 29.1			48
140	{6-chloro-1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		8.9		321	72.7

Row	Compound	Agonist EC50 (nM) CD11b	CD11b agonist activity at 10 uM	CD11B Antagonist Activity IC50 (nM) in 10 Percent Human Plasma	CD11B Antagonist Activity IC50 (nM) CD11b	CD11b Antagonist Activity at 10uM
141	{6-chloro-1-[(6-chloropyridin-3-yl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid		0		593	
142	{6-chloro-1-[3-(difluoromethoxy)benzyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid			1000, 969	7, 5	
143	{6-chloro-1-[4-(difluoromethoxy)benzyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	1000				
144	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		0	495, 579	2.4, 3	
145	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid		0	932	8	
146	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		0	597, 479	3.5, 5	
147	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid		0	1400	10, 2	
148	{6-chloro-5-hydroxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid			131	4	
149	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		-0.4, -2.3		112.1	89.9
150	{6-chloro-5-methoxy-1-[4-(methoxycarbonyl)benzyl]-2-methyl-1H-indol-3-yl}acetic acid		0		101, 128	
151	{6-chloro-5-methoxy-2-methyl-1-[2-methyl-1,3-thiazol-4-yl)methyl]-1H-indol-3-yl}acetic acid				101	
152	{6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		0	4924203 (n=10)	3.3±1 (n=15)	
153	{6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid		9.2	1158	4, 9	
154	{6-chloro-5-methoxy-2-methyl-1-[4-(methylsulfonyl)benzyl]-1H-indol-3-yl}acetic acid		0		1000	
155	{6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		46.8			
156	{6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		2.4, 6.3		102	80.1
157	{6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid		0		110	
158	{6-fluoro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		0	662, 808	<0.1, 8, 9	
159	{6-fluoro-5-hydroxy-2-methyl-1-[3-methyl-2-thienyl]carbonyl]-1H-indol-3-yl}acetic acid		-0.4		393.4	89.9
160	{6-fluoro-5-hydroxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzyl]-1H-indol-3-yl}acetic acid		32.2, 46.8			37
161	{6-fluoro-5-hydroxy-2-methyl-1-[4-(methylthio)benzyl]-1H-indol-3-yl}acetic acid		64.1			
162	{6-fluoro-5-methoxy-2-methyl-1-[3-methyl-2-thienyl]carbonyl]-1H-indol-3-yl}acetic acid		3.8		466.1	89.9
163	{6-fluoro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid		0	1308	12	
164	{6-fluoro-5-methoxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzyl]-1H-indol-3-yl}acetic acid		46			
165	{6-fluoro-5-methoxy-2-methyl-1-[4-(methylthio)benzyl]-1H-indol-3-yl}acetic acid		89.74			
166	{6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	-100				
167	{6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	478				
168	1-[1,3-benzothiazol-2-yl)methyl]-5-fluoro-2-methyl-1H-indole-3-carboxylic acid		0		>1uM	
169	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-piperidin-1-ylacetamide		0		>10000	
170	3-[1-(1,3-benzothiazol-2-yl)methyl]-4,6-dichloro-2-methyl-1H-indol-3-yl]propanoic acid		0	>10 uM	29	
171	3-[1-(1,3-benzothiazol-2-yl)methyl]-6-chloro-2,5-dimethyl-1H-indol-3-yl]propanoic acid		0		249	
172	3-[1-(1,3-benzothiazol-2-yl)methyl]-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid		0		194	
173	3-[4,6-dichloro-1-(3-chlorobenzyl)-2-methyl-1H-indol-3-yl]propanoic acid		33.3		57	
174	3-[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid		16.2	>10 uM	39	
175	3-[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]propanoic acid		0	>10 uM	31, 175, 209, 176	

Kov	Compound	Agonist EC50 (nM) CD11b	CD11b agonist activity at 10 nM	CD11B Antagonist Activity IC50 (nM) in 10 Percent Human Plasma	CD11B Antagonist Activity IC50 (nM) CD11b	CD11b Antagonist Activity at 10nM
176	4-([3-(carboxymethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-1-yl]methyl)benzoic acid		8.3		>10000	
177	5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indole-3-carbaldehyde		2.7		>1000, >10nM	
178	6-chloro-2,3-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indole acetate			462	3, 3	
179	ethyl [1-[4-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	>1000				
180	methyl [1-[4-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	>1000				
181	methyl [1-[4-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	>1000				
182	propyl [1-[4-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	>1000				

FIGURE 8A

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (uM)	DAO % Inhibition at 10 uM
1	control - DAO 1H-indole-2-carboxylic acid			0.42±0.21 (n=6)	96
2	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid				30
3	(1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid				-2.4
4	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0	11.9		-34.4
5	(1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0	0	38.1	39.2
6	(1-benzyl-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	0, 0	7.54		-8.3
7	(1-benzyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	0, 0	20	5.86	36.3, 47.8
8	(1-benzyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0	39.59		5.8
9	(1-methyl-1H-indol-3-yl)oxoacetic acid				-36.3
10	(2E)-2-[4-(dimethylamino)benzylidene]-1-benzothiophen-3(2H)-one				-25.5
11	(2E)-3-(1H-indol-3-yl)acrylic acid				6.4
12	(2E)-3-(5-chloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acrylic acid				-26.7
13	(2E)-3-(5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acrylic acid		16.8		
14	(2E)-3-(5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl)acrylic acid				-54.1
15	(2S)-indoline-2-carboxylic acid			8.26	43.6
16	(2Z)-2-(2-hydroxy-5-methylbenzylidene)-1-benzothiophen-3(2H)-one				-24.2
17	(2Z)-2-(2-thienylmethylene)-2,3-dihydro-1-benzofuran-3-ol				-41.8
18	(3S)-2,3,4,9-tetrahydro-1H-0-carboline-3-carboxylic acid				-2.96
19	(3Z)-5-ethoxy-1H-indole-2,3-dione 3-oxime				-14.6
20	(4Z)-4-(hydroxyimino)-4,5,6,7-tetrahydro-1-benzofuran-2-carboxylic acid				-33.5
21	(5-bromo-1H-indol-3-yl)acetic acid				4.1
22	(5-chloro-2-methyl-1H-indol-3-yl)acetic acid				-23.59
23	(5-fluoro-2-methyl-1H-indol-3-yl)acetic acid		9.8		-28
24	(3-hydroxy-1H-indol-3-yl)acetic acid			3.83	52.4
25	(5-methoxy-1H-indol-3-yl)acetic acid				-40.2
26	(5-methyl-1-benzothien-3-yl)acetic acid				-60.71
27	(6-chloro-1-([(4-chlorophenyl)amino]carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	0	22.2		-3.25
28	(6-chloro-5-methoxy-2-methyl-1-[4-[(trifluoromethylthio)benzoyl]-1H-indol-3-yl)acetic acid		10.7		-16.1
29	(6-chloro-5-methoxy-2-methyl-1-[4-[(trifluoromethylthio)benzoyl]-1H-indol-3-yl)acetic acid	0	32.6, 22.8		-13
30	(6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid				-39.7
31	(6-fluoro-5-hydroxy-2-methyl-1-[4-[(trifluoromethylthio)benzoyl]-1H-indol-3-yl)acetic acid	0, 3.2	10.97		26.6
32	(6-fluoro-5-methoxy-2-methyl-1-[4-[(trifluoromethylthio)benzoyl]-1H-indol-3-yl)acetic acid	0	26		-5.2
33	(6-fluoro-5-methoxy-2-methyl-1-[4-[(trifluoromethylthio)benzoyl]-1H-indol-3-yl)acetic acid	0	14		-48
34	[1-(1,3-benzothiazol-2-ylmethyl)-4-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	17.8		2.99
35	[1-(1,3-benzothiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl]oxoacetic acid	0	0		

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (uM)	DAO % Inhibition at 10 uM
36	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-dimethyl-1H-indol-3-yl]acetic acid	0	19.5		-31.52, 6.1
37	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	0	0		
38	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	1.6	0		-17.5
39	[1-(1,3-benzothiazol-2-ylmethyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	22.5		-63.5
40	[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-12.92
41	[1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0	14.2		-1.9
42	[1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	20.5		-31.2
43	[1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	11.99		0.3
44	[1-(2-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				12.02
45	[1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	0		21.7, 14.6
46	[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	9.56		-9.9
47	[1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		28.6
48	[1-(2,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	14.6		-52.4
49	[1-(3-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	24.3, 0		
50	[1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	8.5		15.3
51	[1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	20.33		-23
52	[1-(4-bromobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				0.9
53	[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				7
54	[1-(4-bromobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	18.84	2.92	36.7
55	[1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-16.8
56	[1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	0	1.22	49.6
57	[1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	13.85		-15.7
58	[1-(4-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	14.6		
59	[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-19.09
60	[1-(4-chlorobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				0.9
61	[1-(4-chlorobenzoyl)-4-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid			46.84	30.6, 38.3
62	[1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-5.5
63	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				22.4
64	[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				19.3
65	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				4, -12
66	[1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	0, 0.2	6.44		
67	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid			2.56	40.3
68	[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	0		-19.6
69	[1-(4-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		-20.8
70	[1-(4-ethylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-49.5

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (nM)	DAO % Inhibition at 10 nM
71	[1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				32
72	[1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-40.9
73	[1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	19.5		-62.8
74	[1-(4-tert-butylbenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-14.4
75	[1-(biphenyl-2-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	39.1		
76	[1-(biphenyl-4-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	19.9		-51.13
77	[1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-0.6
78	[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				-7.9
79	[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		-15.8
80	[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		-48.6
81	[1-(tert-butoxycarbonyl)-1H-indol-2-yl]boronic acid				-118.23
82	[3-(1,3-benzothiazol-2-ylmethyl)-1H-indol-1-yl]acetic acid				7.46
83	[4-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-25.1
84	[4-chloro-1-(4-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid				-27.64
85	[5-fluoro-1-(4-fluorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid	0, 0.7	0		-48.2
86	[5-hydroxy-2-methyl-1-(3-methylbenzoyl)-1H-indol-3-yl]acetic acid				-27
87	[5-hydroxy-2-methyl-1-(3-phenylprop-2-ynyl)-1H-indol-3-yl]acetic acid	0, 0	15.1		6.1
88	[5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid				23.3, 3.3
89	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	0	20.9		23.3
90	[5-methoxy-1-(4-methoxybenzoyl)-2-methyl-1H-indol-3-yl]acetic acid	0	0		-16.6
91	[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	0	0		-29.1
92	[6-chloro-1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		
93	[6-chloro-1-(2,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0			-19.7
94	[6-chloro-1-(2,5-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	82.7, 74		-4.12
95	[6-chloro-1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	50.5, 21.7		-35.53
96	[6-chloro-1-(2-chloro-6-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	24.9		
97	[6-chloro-1-(2'-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	6.6, 0, 0	48.3		
98	[6-chloro-1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		
99	[6-chloro-1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	29.6		
100	[6-chloro-1-(3,5-dichlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	0	50.5, 9.1, 15		
101	[6-chloro-1-(3,5-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		
102	[6-chloro-1-(3,5-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-38
103	[6-chloro-1-(3,5-dimethylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	21		
104	[6-chloro-1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	20.7		-9.1
105	[6-chloro-1-(3-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	0	23.4		-1.27, 12.9

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (uM)	DAO % Inhibition at 10 uM
106	[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	0			8.94
107	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0.1, 0	54.73		-6.47
108	[6-chloro-1-(3-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		-6.24
109	[6-chloro-1-(3-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-27.00, -0.9
110	[6-chloro-1-(4-chloro-2-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				0.49
111	[6-chloro-1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid				-16.3
112	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				-29
113	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-75.3, -46.84
114	[6-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid	2.8	19.74		-10.37
115	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0	16.4	10.4, 7.65	50.19
116	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	0		-61.6, -22.62
117	[6-chloro-1-(4-chlorophenyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				10.99
118	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				-5.8
119	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				11.7
120	[6-chloro-5-methoxy-1-(3-methoxybenzyl)-2-methyl-1H-indol-3-yl]acetic acid				-11.54
121	[6-chloro-5-methoxy-2-methyl-1-(2-naphthylmethyl)-1H-indol-3-yl]acetic acid	0	22.5		-11.5
122	[6-chloro-5-methoxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid	0	0		-23.87, 6.4
123	[6-chloro-5-methoxy-2-methyl-1-(3-nitrobenzyl)-1H-indol-3-yl]acetic acid				-33
124	[6-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylmethyl)-1H-indol-3-yl]acetic acid	0	13.3		-79.1
125	[6-chloro-5-methoxy-2-methyl-1-(quinolin-2-ylmethyl)-1H-indol-3-yl]acetic acid	0	18.9		-50.6
126	[6-fluoro-1-(4-fluorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				1.7
127	[6-fluoro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				16.7
128	[6-fluoro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		18.17
129	[6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	0	0, 0	27.73, 27.37	42.6
130	[6-fluoro-5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid				24.2
131	[6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	0	5.5		-4.7
132	[6-fluoro-5-methoxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetic acid				-9.7
133	[1-[(4-chlorophenyl)sulfonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	0		-38.6
134	[1-[(4-chlorophenyl)sulfonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0, 0	27.53		-16.7
135	[1-[(4-chlorophenyl)sulfonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	0	20.6		-19.7
136	[1-[(5-chloro-2-thienylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0	0	13.93	39.3
137	[1-[(5-chloro-2-thienylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		1		-14.4
138	[1-[(5-chloro-2-thienylcarbonyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	0	0		25.9
139	[1-[(5-chloro-2-thienylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		0		-15.2
140	[1-[(5-chloro-2-thienylmethyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid		19.24		1.3

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (nM)	DAO % Inhibition at 10 nM
141	{1-[(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	0	0	7.3, 4.95	51.6
142	{1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	0	26.3		2.3
143	{1-[(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid				-1.4
144	{1-[(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid				-18.9
145	{1-[3,5-bis(trifluoromethyl)benzyl]-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	0	19		
146	{1-[4-(difluoromethoxy)benzyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid				-3.7
147	{1-[4-(difluoromethoxy)benzyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid				-56.8
148	{1-[4-(difluoromethoxy)benzyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid				0.3
149	{1-[4-(difluoromethoxy)benzyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid				-13.4
150	{2-chloro-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	5		-52.1
151	{2-chloro-3-[3-(trifluoromethoxy)benzyl]-1H-indol-1-yl}acetic acid	0	0		
152	{2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	13		
153	{2-oxo-1-[3-(trifluoromethoxy)benzyl]-2,3-dihydro-1H-indol-3-yl}acetic acid	0	20		-69.3
154	{4,6-dichloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	0		
155	{5,6-dichloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	30		-23.5
156	{5-chloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	24		-39.3
157	{5-chloro-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	0	21		-43.3
158	{5-fluoro-1-[3-(trifluoromethoxy)benzyl]-1H-indol-2-yl}(oxo)acetic acid	0			
159	{5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}(oxo)acetic acid	0	0		
160	{5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	12		-45.3
161	{5-fluoro-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0, 8.8	0		-35.5
162	{5-hydroxy-2-methyl-1-[(2E)-3-phenylprop-2-enoyl]-1H-indol-3-yl}acetic acid	0, 0	11.93		-24.2
163	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				15.9
164	{5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		7.7	4.77, 4.77	48.4
165	{5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid				-10.8
166	{5-methoxy-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	20		
167	{5-methoxy-2-methyl-1-[(2E)-3-phenylprop-2-enoyl]-1H-indol-3-yl}acetic acid	0.5	0		-66.7
168	{5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid		20.5		
169	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				-53.5
170	{5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	10.5		-21.9
171	{5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid				19.5
172	{6-chloro-1-[4-(chlorophenoxy)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	0	14.2		-63.3
173	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid	0	32.2, 8.6		-25.6
174	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	0	0		32.6
175	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	0	0		-1.8

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (nM)	DAO % Inhibition at 10 nM
176	{6-chloro-1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	25			-1.4
177	{6-chloro-1-[(6-chloropyridin-3-yl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	0	29.4		6.17, -37.93
178	{6-chloro-1-[3-(difluoromethoxy)benzyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	0	20		
179	{6-chloro-1-[4-(difluoromethoxy)benzyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid				-73.3
180	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0, 0	0, 0		2.2
181	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	0		9.1
182	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	0		
183	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	0		
184	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				20.2
185	{6-chloro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	0	18.75, 18.75	41.2
186	{6-chloro-5-methoxy-2-methyl-1-[4-(methoxycarbonyl)benzyl]-2-methyl-1H-indol-3-yl}acetic acid	0	11.5		
187	{6-chloro-5-methoxy-2-methyl-1-[2-methyl-1,3-thiazol-4-yl)methyl]-1H-indol-3-yl}acetic acid				-14.81
188	{6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	27.5		-10.21
189	{6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	0	17.2		2.04, 0.5
190	{6-chloro-5-methoxy-2-methyl-1-[4-(methylsulfonyl)benzyl]-1H-indol-3-yl}acetic acid	0	0		-10.69
191	{6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				-26.6
192	{6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	19		-17.4
193	{6-fluoro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	0		
194	{6-fluoro-5-hydroxy-2-methyl-1-[5-methyl-2-thienyl]carbonyl]-1H-indol-3-yl}acetic acid	0	0		12
195	{6-fluoro-5-hydroxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzyl]-1H-indol-3-yl}acetic acid	0	0		23.5
196	{6-fluoro-5-hydroxy-2-methyl-1-[4-(methylthio)benzyl]-1H-indol-3-yl}acetic acid	0	0	83.31	35.7
197	{6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				24.4
198	{6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid				-30.2
199	{6-fluoro-5-methoxy-2-methyl-1-[5-methyl-2-thienyl]carbonyl]-1H-indol-3-yl}acetic acid	0			-18.8
200	{6-fluoro-5-methoxy-2-methyl-1-[3-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid	0			
201	{6-fluoro-5-methoxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzyl]-1H-indol-3-yl}acetic acid				-27.4
202	{6-fluoro-5-methoxy-2-methyl-1-[4-(methylthio)benzyl]-1H-indol-3-yl}acetic acid	0	0		-12.4
203	{6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid				-84.3
204	{6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-1H-indol-3-yl}acetic acid				-50.9
205	1-(2,3-dihydro-1-benzofuran-2-yl)-N,N-dimethylmethanamine hydrochloride				-38.1
206	1-(4,5,6,7-tetrahydro-1-benzothien-2-yl)carbonyl)indoline				-35.5
207	1-(phenylsulfonyl)-1H-indole-3-carbaldehyde				-2.2
208	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride				-12.17
209	1,2,3,4-tetrahydroquinolin-8-ol			2.3	74.56, 64.8
210	1-[2-(dimethylamino)ethyl]-1H-indole-2-carboxylic acid hydrochloride				-95.99

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (nM)	DAO % Inhibition at 10 nM
211	1-benzofuran-2,3-dicarboxylic acid				13.5
212	1-benzofuran-2-carboxylic acid			2.9	46.8, 67.02, 69.1
213	1-benzofuran-2-ylboronic acid				-43.3
214	1-benzothien-2-ylboronic acid				-17.5
215	1-benzothiophene-2-carboxylic acid				10.74
216	1-benzyl-5-methoxy-2-methyl-1H-indole-3-carboxylic acid				-93.77
217	1H-imidazole-2-carboxylic acid			>100	10.1
218	1H-indol-2-yl(pyridin-4-yl)methanol				10.6
219	1H-indol-2-ylmethanol				-11.7
220	1H-indol-3-ylacetic acid				-91.12
221	1H-indole-3-carboxylic acid				-13.2
222	1H-indole-5-carboxylic acid				-9.7
223	1H-indole-6-carboxylic acid				-6.7
224	1H-pyrrole-2-carboxylic acid			1.26, 1.26	71.09
225	1-methyl-1H-indole-2-carboxylic acid				-23, -74.11
226	1-methyl-1H-pyrrole-2-carboxylic acid				-1.34
227	2-(3-hydroxybenzyl)butanoic acid				-59.64
228	2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid				-39.1
229	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-hydroxyethyl)acetamide				-77.7
230	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-phenylethyl)acetamide				0.7
231	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-piperidin-1-ylacetamide	0	11.1		-62.1
232	2-[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetamide				-32.2
233	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethanol				-59.9
234	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl 4-chlorobenzoate				-48.7
235	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl acetate				-68.2
236	2-[[acetyl(isopropylamino)methyl]-6-bromo-4-hydroxy-5-methoxy-1-methyl-1H-indole-3-carboxylic acid			9.94	-12.12, 38.2
237	2-fluoroic acid				-3.48
238	2-hydroxy-3-(1H-indol-3-yl)propanoic acid				-6.62
239	2-methyl-5-[[6-(4-methylphenyl)sulfonylamino]-1-benzofuran-3-carboxylic acid			>100	11.9
240	2-methylimidazo[1,2-a]pyridine-3-carboxylic acid				-50.29, -6.5
241	3-((1E)-[4-(phenylethynyl)phenyl]methylene)amino)-1H-1,2,4-triazole-5-carboxylic acid				-22.11
242	3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1H-1,2,4-triazole-5-carboxylic acid				-41.61
243	3-(1H-benzimidazol-2-yl)propanoic acid				-12.21
244	3-(2-aminoethyl)-5-(aminosulfonyl)-1H-indole-2-carboxylic acid				-7.12
245	3-(2-aminoethyl)-5-ethoxy-1H-indole-2-carboxylic acid				-34.28, -7.8

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (uM)	DAO % Inhibition at 10 uM
246	3-(2-thienyl)-1H-pyrazole-5-carboxylic acid				13.17, 15.6
247	3-(4-methylphenyl)-1H-pyrazole-5-carboxylic acid				-21.88
248	3-(acetylamino)-5-methoxy-1H-indole-2-carboxylic acid				-70.4
249	3-(carboxymethyl)-1H-indole-2,5-dicarboxylic acid				-21
250	3-(carboxymethyl)-1H-indole-2-carboxylic acid				-16.9
251	3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrole-2-carboxylic acid				-32.69
252	3-[1-[1,3-benzothiazol-2-ylmethyl]-4,6-dichloro-2-methyl-1H-indol-3-yl]propanoic acid	0	6.3		-8
253	3-[1-[1,3-benzothiazol-2-ylmethyl]-6-chloro-2,5-dimethyl-1H-indol-3-yl]propanoic acid				-0.9
254	3-[1-[1,3-benzothiazol-2-ylmethyl]-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid	0	0		9.6
255	3-[2-(acetylamino)ethyl]-5-ethoxy-1H-indole-2-carboxylic acid				6.96
256	3-[4,6-dichloro-1-(3-chlorobenzyl)-2-methyl-1H-indol-3-yl]propanoic acid				5.1
257	3-[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid				14.8
258	3-[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]propanoic acid	0	0		-29.07
259	3-anilino-1-benzothiophene-2-carboxylic acid				-60.82
260	3-chloro-1-benzothiophene-2-carboxylic acid				-17.09, 1.1
261	3H-benzof[5]indole-2-carboxylic acid				-59.03
262	3-methyl-4-oxo-6-(2-thienyl)-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid				-3.3
263	4-(benzyloxy)-1H-indole-2-carboxylic acid			0.814	63.30, 79.5
264	4,5,6,7-tetrahydro-1,2-benzisoxazole-3-carboxylic acid				-29.46
265	4-[[[dimethylamino)methyl]-3-[(hydroxy(phenyl)methyl]-1-benzofuran-5-yl]				-11.4
266	4-[3-(4-chlorophenyl)propyl]-1H-pyrrole-2-carboxylic acid			1.3	49.4
267	4-chloro-1H-pyrazole-5-carboxylic acid			3	36.2
268	4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-carboxylic acid				-23.3
269	4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid				-20.5
270	5-(trifluoromethoxy)-1H-indole-2-carboxylic acid				-43.65
271	5,6,7-trimethoxy-1H-indole-2-carboxylic acid				1.7
272	5,7-dichloro-8-hydroxyquinolin-2(1H)-one				-46.17
273	5-[[[4-fluorophenyl)sulfonyl]amino]-2-methyl-1-benzofuran-3-carboxylic acid				-94.3
274	5-butyl-1H-indole-2-carboxylic acid				-28.64
275	5-chloro-1H-indole-2-carboxylic acid			5.6, 5.6	66.6, 54.54, 74.28
276	5-chloro-3-phenyl-1-benzofuran-2(3H)-one			20.6, 6.19	43.9
277	5-ethyl-1H-indole-2-carboxylic acid			3.24	5.95
278	5-ethyl-3-phenyl-1-benzofuran-2(3H)-one				28.7
279	5-fluoro-1-benzothiophene-2-carboxylic acid				-23.07
280	5-fluoro-1H-indole-2-carboxylic acid			0.38, 0.38	93.5, 72.9

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (uM)	DAO % Inhibition at 10 uM
281	5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indole-3-carbaldehyde		16.9		
282	5-fluoro-2-methyl-1H-indole-3-carbaldehyde				-17.7
283	5-hydroxy-1-(4-methoxyphenyl)-2-methyl-1H-indole-3-carboxylic acid			8.48	39.6
284	5-hydroxy-1H-indole-2-carboxylic acid			1.07, 1.07	60.5
285	5-hydroxy-1H-indole-3-carboxylic acid			4.5, 0.93	58.7
286	5-hydroxy-2-methylnaphtho[1,2-b]furan-3-carboxylic acid			7.7	53.68, 47.6
287	5-isopropyl-1H-indole-2-carboxylic acid				-89.92
288	5-methoxy-1H-indole-2-carboxylic acid				11.5, -53.87
289	5-methoxy-3-methyl-1-benzofuran-3-carboxylic acid				-80.08
290	5-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid				-9.21
291	5-methylthiophene-2-carboxylic acid			2.75	54.90, 65.3
292	5-oxo-L-proline				-66.7, 9.0
293	5-phenyl-2-furvic acid				-8.71
294	5-sec-butyl-1H-indole-2-carboxylic acid				-105.3
295	5-tert-butyl-1H-indole-2-carboxylic acid				-104.48
296	6-benzyl-7-hydroxy-5-methyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carboxylic acid				-83.55
297	6-chloro-2,3-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indole acetate				-16.4
298	6-ethyl-1H-indole-2-carboxylic acid				-49.82
299	6-hydroxy-3-methyl-1-benzofuran-2-carboxylic acid			4.68	16.56, 48.0
300	6-isopropyl-1H-indole-2-carboxylic acid				-117.39
301	7-hydroxy-1-benzothiophene-2-carboxylic acid				18.1
302	7-methoxy-1-benzothiophene-2-carboxylic acid				-9.8
303	8-bromo-6-hydroxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid			7.7	47.64, 50.1
304	9-nitro-4-propyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid				9.57
305	butyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				-18.8
306	ethyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				-40.9
307	ethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				-43.4
308	ethyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				-24.4
309	ethyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				-38.2
310	ethyl 1-butyl-5-hydroxy-2-methyl-4-[(4-methylpiperazin-1-yl)methyl]-1H-indole-3-carboxylate			20.44	35.2
311	ethyl 2-(acetylamino)-7-methoxy-1-benzothiophene-3-carboxylate				-19.6
312	ethyl 2-methyl-1H-indole-3-carboxylate				-6.8
313	ethyl 4-[[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetyl]amino]butanoate				-2.5
314	ethyl 4-[(dimethylamino)methyl]-5-hydroxy-1-(4-methoxyphenyl)-2-methyl-1H-indole-3-carboxylate hydrochloride			42.8	
315	ethyl 4-[(dimethylamino)methyl]-5-hydroxy-1,2-dimethyl-1H-indole-3-carboxylate hydrochloride			21.46, 8.5	37.6

Row	Compound	cAMP (DP-1) Agonist % Inhibition	cAMP (DP-1) Antagonist % Inhibition	DAO IC50 (uM)	DAO % Inhibition at 10 uM
316	ethyl 4-amino-3-(aminocarbonyl)isothiazole-5-carboxylate				2.04
317	ethyl 5-hydroxy-2-methyl-1H-indole-3-carboxylate			4.8	45.4
318	ethyl 7-methoxy-1H-indole-2-carboxylate				-15.6
319	ethyl N-([1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl)glycinate				-50.7
320	ethyl N-([1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetyl)glycinate				1.1
321	ethyl N-([6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl)glycinate				-29.6
322	indoline-2-carboxylic acid			2.88, 7.88	37.34
323	isopropyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				10.3
324	methyl [(3-nitro-1H-indol-2-yl)thio]acetate				-28.4
325	methyl [(5-fluoro-3-nitro-1H-indol-2-yl)thio]acetate				-37.3
326	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				-8.3
327	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate				-25.2
328	methyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				-12.8
329	methyl 1H-indole-3-carboxylate				-2.3
330	methyl 3-amino-6-methylthieno[2,3-b]pyridine-2-carboxylate				-11.9
331	methyl 4,6-dimethoxy-1H-indole-2-carboxylate				0.1
332	methyl 4-methoxy-1H-indole-2-carboxylate				-6
333	methyl 6-methoxy-1H-indole-2-carboxylate				-8.2
334	methyl N-([1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetyl)-D-alaninate				-6
335	N-([1H-indol-3-ylacetyl])-L-alanine				-15.7
336	N-[3-hydroxy-2-oxo-3-(trifluoromethyl)-2,3-dihydro-1-benzofuran-6-yl]acetamide				-3.7
337	N-([1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl)glycine				-60.3
338	N-([6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl)glycine				-38.1
339	proline				-16.17
340	propyl [5-hydroxy-2-methyl-1H-indol-3-yl]acetate			1.1, 1.1, 1.87	62.9, 50.57
341	propyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				-26.2
342	propyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				-1.2
343	quinoline-2,8-diol			14.66	31.6
344	sec-butyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				-0.4
345	sec-butyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				-19.4, -2.7
346	sec-butyl [6-chloro-1-[4-(difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetate				-28.5
347	sodium (5E)-5-[(aminocarbonylhydrazono)-1-methyl-6-oxo-2,3,5,6-tetrahydro-1H-indole-2-sulfonate trihydrate				-5.1
348	sodium 6-methoxy-1,3-benzothiazole-2-carboxylate				-28.38, -16.3

FIGURE 8B

Row	IUPAC Name	Pig DAO % Inhibition 10uM	Pig DAO IC50 (uM)	Human DAO % Inhibition (10 uM)	Human DAO IC50 (uM)
1	(2E)-2-(2-furylmethylene)-1-benzothiophen-3(2H)-one	0	not determined	not determined	not determined
2	(2E)-2-[4-(dimethylamino)benzylidene]-1-benzothiophen-3(2H)-one	0	not determined	not determined	not determined
3	(2E)-5-nitro-3H-3H-2,2'-bi-1-benzothiophene-3,3'-dione	0	not determined	not determined	not determined
4	(2R)-indoline-2-carboxylic acid	not determined	not determined	50-100	<1
5	(2S)-indoline-2-carboxylic acid	10-50	not determined	10-50	<1
6	(2Z)-2-(2-hydroxy-5-methylbenzylidene)-1-benzothiophen-3(2H)-one	0	not determined	not determined	not determined
7	(2Z)-2-(2-thienylmethylene)-2,3-dihydro-1-benzofuran-3-ol	0	not determined	0	not determined
8	(2Z)-2-(3-ethoxy-2-hydroxybenzylidene)-1-benzothiophen-3(2H)-one	0	not determined	not determined	not determined
9	(3Z)-5-ethoxy-1H-indole-2,3-dione 3-oxime	0	not determined	0	not determined
10	(4Z)-4-(hydroxyimino)-4,5,6,7-tetrahydro-1-benzofuran-2-carboxylic acid	0	not determined	not determined	not determined
11	(5-methyl-1-benzothien-3-yl)acetic acid	0	not determined	0	not determined
12	(2-oxo-1-[3-(trifluoromethoxy)benzyl]-2,3-dihydro-1H-indol-3-yl)acetic acid	0	not determined	not determined	not determined
13	1-(2,3-dihydro-1-benzofuran-2-yl)-N,N-dimethylmethanamine hydrochloride	0	not determined	not determined	not determined
14	1-(4,5,6,7-tetrahydro-1-benzothien-2-ylcarbonyl)indoline	0	not determined	0	not determined
15	1,2,3,4-tetrahydroisquinoline-3-carboxylic acid hydrochloride	0	not determined	not determined	not determined
16	1,2,3,4-tetrahydroquinolin-8-ol	50-100	1-10	50-100	<1
17	1-benzofuran-2,3-dicarboxylic acid	10-50	not determined	0	not determined
18	1-benzofuran-2-carboxylic acid	50-100	1-10	not determined	1-10
19	1-benzofuran-2-boronic acid	0	not determined	not determined	not determined
20	1-benzothien-2-ylboronic acid	0	not determined	not determined	not determined
21	1-benzothienophene-2-carboxylic acid	10-50	not determined	not determined	not determined
22	1H-benzimidazole-2-carboxylic acid hydrate	not determined	not determined	50-100	not determined
23	1H-benzimidazole-2-sulfonic acid	1-10	not determined	not determined	not determined
24	1H-indazole-3-carboxylic acid	0	not determined	10-50	not determined
25	1H-pyrrolo[2,3-b]pyridine 7-oxide	not determined	not determined	1-10	not determined
26	1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid	not determined	not determined	50-100	<1
27	1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid	not determined	not determined	10-50	not determined
28	1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid	not determined	not determined	50-100	1-10
29	1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid	not determined	not determined	50-100	1-10
30	2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid	0	not determined	not determined	not determined
31	2-methyl-5-[(4-methylphenyl)sulfonyl]amino-1-benzofuran-3-carboxylic acid	10-50	>100	0	not determined
32	2-methylimidazo[1,2-a]pyridine-3-carboxylic acid	0	not determined	0	not determined
33	3-(1H-benzimidazol-2-yl)propanoic acid	0	not determined	not determined	not determined
34	3-amino-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylic acid	10-50	10-50	50-100	10-50
35	3-amino-6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzothioephene-2-carboxamide	0	not determined	not determined	not determined
36	3-amino-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxylic acid	0	not determined	0	not determined
37	3-anilino-1-benzothioephene-2-carboxylic acid	0	not determined	0	not determined
38	3-chloro-1-benzothioephene-2-carboxylic acid	<1	not determined	0	not determined
39	3H-benzo[e]indole-2-carboxylic acid	0	not determined	0	not determined
40	4-[(dimethylamino)methyl]-3-[hydroxy(phenyl)methyl]-1-benzofuran-5-ol	0	not determined	10-50	not determined
41	4-isopropyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid	0	not determined	10-50	not determined

Row	IUPAC Name	Pig DAO % Inhibition 10uM	Pig DAO IC50 (uM)	Human DAO % Inhibition (10 uM)	Human DAO IC50 (uM)
42	4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-carboxylic acid	0	not determined	not determined	not determined
43	4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid	0	not determined	not determined	not determined
44	5-(carboxymethoxy)-2-methyl-1-benzofuran-3-carboxylic acid	0	not determined	0	not determined
45	5,7-dichloro-8-hydroxyquinolin-2(1H)-one	0	not determined	10-50	not determined
46	5-[(4-fluorobenzyl)oxy]-2-phenyl-1-benzofuran-3-carboxylic acid	0	not determined	0	not determined
47	5-[(4-fluorophenyl)sulfonylamino]-2-methyl-1-benzofuran-3-carboxylic acid	0	not determined	0	not determined
48	5-bromo-1,3-dihydro-2H-pyrido[2,3-b]pyridin-2-one	not determined	not determined	10-50	not determined
49	5-chloro-3-phenyl-1-benzofuran-2(3H)-one	10-50	10-50	10-50	not determined
50	5-ethyl-3-phenyl-1-benzofuran-2(3H)-one	10-50	not determined	10-50	not determined
51	5-fluoro-1-benzothiophene-2-carboxylic acid	0	not determined	1-10	not determined
52	5-hydroxy-2-phenyl-1-benzofuran-3-carboxylic acid	0	not determined	1-10	not determined
53	5-methoxy-2-methyl-1-benzofuran-3-carboxylic acid	0	not determined	0	not determined
54	5-methoxy-2-methyl-2,3-dihydro-1-benzofuran-6-carbaldehyde	0	not determined	not determined	not determined
55	6-bromo-2-tert-butyl-5-hydroxy-1-benzofuran-3-carboxylic acid	0	not determined	10-50	not determined
56	6-hydroxy-3-methyl-1-benzofuran-2-carboxylic acid	10-50	1-10	10-50	not determined
57	7-hydroxy-1-benzothiophene-2-carboxylic acid	10-50	not determined	10-50	not determined
58	7-methoxy-1-benzothiophene-2-carboxylic acid	0	not determined	0	not determined
59	9-bromo-6-hydroxy-3a,4,5,8b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid	10-50	1-10	50-100	not determined
60	decahydroquinoline-2-carboxylic acid	not determined	not determined	0	not determined
61	ethyl 1H-pyrrolo[3,2-b]pyridine-2-carboxylate 4-oxide	not determined	not determined	10-50	not determined
62	ethyl 1H-pyrrolo[3,2-b]pyridine-2-carboxylate	not determined	not determined	0	not determined
63	ethyl 1H-pyrrolo[3,2-b]pyridine-2-carboxylate 5-oxide	not determined	not determined	10-50	not determined
64	ethyl 2-(acetamido)-7-methoxy-1-benzothiophene-3-carboxylate	0	not determined	0	not determined
65	ethyl 3-amino-1-methyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate	0	not determined	0	not determined
66	ethyl imidazo[1,2-a]pyridine-2-carboxylate	not determined	not determined	<1	not determined
67	imidazo[1,2-a]pyridine-2-carboxylic acid	not determined	not determined	10-50	not determined
68	indoline-2-carboxylic acid	10-50	1-10	50-100	not determined
69	methyl 3-amino-6-methylthio[2,3-b]pyridine-2-carboxylate	0	not determined	0	not determined
70	methyl indoline-2-carboxylate	not determined	not determined	10-50	not determined
71	methyl pyrazolo[1,5-a]pyridine-2-carboxylate	not determined	not determined	0	not determined
72	N-(benzoyloxy)-N-methylindoline-2-carboxamide	not determined	not determined	50-100	not determined
73	N-(1-(1-benzothien-2-yl)ethyl)-N-hydroxyurea	10-50	not determined	not determined	not determined
74	N-hydroxyindoline-2-carboxamide	not determined	not determined	50-100	1-10
75	N-hydroxy-N-methylindoline-2-carboxamide	not determined	not determined	10-50	10-50
76	N-methylindoline-2-carboxamide	not determined	not determined	0	not determined
77	pyrazolo[1,5-a]pyridine-2-carboxylic acid	not determined	not determined	10-50	not determined
78	quinoline-2,8-diol	10-50	50-100	10-50	not determined
79	quinoline-2-carboxylic acid	not determined	not determined	0	not determined
80	quinoline-2-carboxylic acid	not determined	not determined	1-10	not determined
81	sodium (5E)-5-[(aminocarbonyl)hydrazono]-1-methyl-6-oxo-2,3,5,6-tetrahydro-1H-indole-2-sulfonate trihydrate	0	not determined	0	not determined
82	sodium 6-methoxy-1,3-benzothiazole-2-carboxylate	0	not determined	0	not determined

Row	IUPAC Name	Pig DAO % Inhibition 10uM	Pig DAO IC50 (uM)	Human DAO % Inhibition (10 uM)	Human DAO IC50 (uM)
83	indoline-2-carbohydrazide	not determined	not determined	50-100	1-10

FIGURE 9A

Row	Compound	FAAH Rat brain AMICAA IC50 (um)	FAAH Rat brain AMICAA Percent Inhibition (0.1 uM)	FAAH Rat brain AMICAA Percent Inhibition (1 uM)	RAT Brain FAAH IC50 (uM)	RAT Brain FAAH Percent Inhibition @ 0.1 uM	RAT Brain FAAH Percent Inhibition @ 1 uM	Human Brain FAAH Percent Inhibition	Human Brain FAAH IC50 (uM)
1	control - indomethacin	9.2, 9.3, 13.1			16.75 ± 9.12 (n=10)				80.15, 77.08, 100
2	control - benorolac				61.56				63.7 ± 4.5, 106 ± 13.86 ± 29
3	control URB 597 (3'-(aminocarbonyl)N-phenyl-3-yl cyclohexylcarbamate)				0.01	92, 97	99, 100		0.053, 0.042 ± 0.0135, 0.13 ± 0.043, 0.019 ± 0.0025
4	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid							7.39	
5	(1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							16.93	
6	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							30.86, -3.75	106.5
7	(1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid							13.43	
8	(1-benzoyl-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid							2.59	
9	(1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid							-19.63 -11.35	
10	(1-benzoyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							6.5	
11	(6-chloro-1-[(4-chlorophenyl)amino]carbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							12.1	
12	(6-chloro-5-methoxy-2-methyl-1-[(4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid							3.2	
13	(6-chloro-5-methoxy-2-methyl-1-[(4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid							21.54	
14	(6-fluoro-5-hydroxy-2-methyl-1-[(4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid							-10	
15	(6-fluoro-5-methoxy-2-methyl-1-[(4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid							15.59	
16	(6-fluoro-5-methoxy-2-methyl-1-[(4-(trifluoromethyl)thio]benzoyl)-1H-indol-3-yl)acetic acid							26.26	
17	[1-(1,3-benzothiazol-2-yl)methyl]-4-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							14.4	
18	[1-(1,3-benzothiazol-2-yl)methyl]-6-chloro-2,5-dimethyl-1H-indol-3-yl)acetic acid							19.0 ± 0.8	
19	[1-(1,3-benzothiazol-2-yl)methyl]-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid							7.8	
20	[1-(1,3-benzothiazol-2-yl)methyl]-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							25.69, 16.6, 15.6	
21	[1-(1,3-benzothiazol-2-yl)methyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							7	
22	[1-(1,3-benzothiazol-2-yl)methyl]-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							9.2	
23	[1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid							10.94	
24	[1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid							16.77, 31.08	
25	[1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid							7.49, 25.9	

Row	Compound	FAAH Rat brain AMICAA IC50 (µM)	FAAH Rat brain AMICAA Percent Inhibition (0.1µM)	FAAH Rat brain AMICAA Percent Inhibition (1µM)	RAT Brain FAAH IC50 (µM)	RAT Brain FAAH Percent Inhibition @ 0.1µM	RAT Brain FAAH Percent Inhibition @ 1µM	Human Brain FAAH (10µM) Percent Inhibition	Human Brain FAAH IC50 (µM)
26	[1-(2-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							7.4	
27	[1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							16.87	
28	[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							18.88	
29	[1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							8.38	
30	[1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							10.01	
31	[1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							5.75	
32	[1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							7.76	
33	[1-(4-bromobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							14.07	
34	[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							23.87	
35	[1-(4-bromobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							18	
36	[1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							29.09, -9.6	
37	[1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							21.78	
38	[1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							15.17	
39	[1-(4-bromobenzoyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							18.0, 18.0	
40	[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							21.9	
41	[1-(4-chlorobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							21.05	
42	[1-(4-chlorobenzoyl)-4-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							18.04	
43	[1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							17.39	
44	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		9.1, 6.1	13.3, 4.3		4.5	2.6		161 ± NA
45	[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid		12.8, 1.3	7.5, 0.6	81.3, 51.67, 81	-2.3	0.3		59.39, 73 ± 18
46	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid		2, 7.6	11.3, 2.6	26.1	14.2	10.1		57 ± 11
47	[1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid							4	
48	[1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							20.8	
49	[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				32.2			21	
50	[1-(4-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							1.07	

Row	Compound	FAAH Rat brain AMCAA IC50 (um)	FAAH Rat brain AMCAA Percent Inhibition (0.1 uM)	FAAH Rat brain AMCAA Percent Inhibition (1 uM)	RAT Brain FAAH Inhibition @ 0.1uM	RAT Brain FAAH Percent Inhibition @ 1uM	Human Brain FAAH (10uM) Percent Inhibition	Human Brain FAAH IC50 (uM)
51	[1-(4-ethylbenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						42.32, 42.22	29.5
52	[1-(4-fluorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid						7.89	
53	[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						21.93	
54	[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						18.2	
55	[1-(4-tert-butylbenzyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						21	
56	[1-(4-phenyl-3-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						10.4	
57	[1-(4-phenyl-4-ylmethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						1.1	
58	[1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						-2.55	
59	[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid						20.23	
60	[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						21.71, 23.49	
61	[1-(cyclohexylcarbonyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						10.44	
62	[4-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						13.04	
63	[4-chloro-1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid						6.6	
64	[5-fluoro-1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]acetic acid						-8	
65	[5-hydroxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid						19.89	
66	[5-hydroxy-2-methyl-1-(3-phenylprop-2-ynyl)-1H-indol-3-yl]acetic acid						3.38	
67	[5-hydroxy-2-methyl-1-(4-methylbenzyl)-1H-indol-3-yl]acetic acid						18.34	
68	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid						7.28	
69	[5-methoxy-1-(4-methylbenzyl)-2-methyl-1H-indol-3-yl]acetic acid						34.93, 6.4	59
70	[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid						5.91, 25.18	
71	[6-chloro-1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						23.1, 23.1	
72	[6-chloro-1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						20.8	
73	[6-chloro-1-(2,6-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						4.3	
74	[6-chloro-1-(2-chloro-4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						10.6	
75	[6-chloro-1-(2-chloro-6-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid						-9.8	

Row	Compound	FAAH Rat brain AMICAA IC50 (uM)	FAAH Rat brain AMICAA Percent Inhibition (0.1uM)	FAAH Rat brain AMICAA Percent Inhibition (1uM)	RAT Brain FAAH IC50 (uM)	RAT Brain FAAH Percent Inhibition @ 0.1uM	RAT Brain FAAH Percent Inhibition @ 1uM	Human Brain FAAH (10uM) Percent Inhibition	Human Brain FAAH IC50 (uM)
76	[6-chloro-1-(2-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							16.4	
77	[6-chloro-1-(3,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							36.28, 5.83	35
78	[6-chloro-1-(3,4-difluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							29.41	
79	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							0.5	
80	[6-chloro-1-(3-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]acetic acid							17.3, 19.0	
81	[6-chloro-1-(3-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid							12.6	
82	[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							18.9, 21.2	
83	[6-chloro-1-(3-cyanobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							6	
84	[6-chloro-1-(3-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							20.6	
85	[6-chloro-1-(4-chloro-2-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							13	
86	[6-chloro-1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid								36, 11
87	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid								66.71
88	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	7.4		18.4	25.9, 21.4, 18.4	9	9		32.26, 62.3 ± 32.5, 27 ± 13, 60 ± 16.5
89	[6-chloro-1-(4-chlorobenzyl)-2,3,5-trimethoxy-2-methyl-1H-indol-3-yl]acetic acid							6.4	
90	[6-chloro-1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							9.9	
91	[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							32.0, 15.5, 18.9	78, 97
92	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							18.41, -16.38	
93	[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							11.2	
94	[6-chloro-1-(cyclohexylmethyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							12.6	
95	[6-chloro-5-methoxy-1-(3-methoxybenzyl)-2-methyl-1H-indol-3-yl]acetic acid							10.5	
96	[6-chloro-5-methoxy-2-methyl-1-(2-naphthylmethyl)-1H-indol-3-yl]acetic acid							8.8	
97	[6-chloro-5-methoxy-2-methyl-1-(3-methylbenzyl)-1H-indol-3-yl]acetic acid							11.2	
98	[6-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylmethyl)-1H-indol-3-yl]acetic acid							-1.8	
99	[6-chloro-5-methoxy-2-methyl-1-(quinolin-2-ylmethyl)-1H-indol-3-yl]acetic acid							10.4	
100	[6-fluoro-1-(4-fluorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							-6.87	

Row	Compound	FAAH Rat brain AMCAA IC50 (um)	FAAH Rat brain AMCAA Percent Inhibition (0.1uM)	FAAH Rat brain AMCAA Percent Inhibition (1uM)	RAT Brain FAAH IC50 (uM)	RAT Brain FAAH Percent Inhibition @ 0.1uM	RAT Brain FAAH Percent Inhibition @ 1uM	Human Brain FAAH (10uM) Percent Inhibition	Human Brain FAAH IC50 (uM)
101	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							6.34	
102	[6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							12.9	
103	[6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid							7.62, -8.22	
104	[6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid							12.89	
105	[1-(4-chlorophenyl)butyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							4.75	
106	[1-(4-chlorophenyl)butyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							15.0 15.29	
107	[1-(4-chlorophenyl)butyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							-3.5	
108	[1-(5-chloro-2-thienylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							3.12	
109	[1-(5-chloro-2-thienylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							-13	
110	[1-(5-chloro-2-thienylcarbonyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							13.98	
111	[1-(5-chloro-2-thienylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							8.11, 14.01	
112	[1-(5-chloro-2-thienylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							0	
113	[1-(5-chloro-2-thienylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							46.42	125, 90
114	[1-(5-chloro-2-thienylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							28.98, -6.47	51
115	[1-(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							8.95	
116	[1-(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							21.58	
117	[1-(4-difluoromethoxy)benzoyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							-2.6	
118	[1-(4-difluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							5.55	
119	[1-(4-difluoromethoxy)benzoyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid				32.8				108, 84
120	[1-(4-difluoromethoxy)benzoyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				87.6				184.7, 135, 157
121	[5-fluoro-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetic acid							7	
122	[5-hydroxy-2-methyl-1-(2E)-3-phenylprop-2-enyl]-1H-indol-3-yl]acetic acid							2.16	
123	[5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetic acid							17.46	
124	[5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetic acid							4.8	
125	[5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetic acid							21.06	

Row	Compound	FAAH Rat brain AMCAA IC50 (nm)	FAAH Rat brain AMCAA Percent Inhibition (0.1 uM)	FAAH Rat brain AMCAA Percent Inhibition (1 uM)	RAT Brain FAAH IC50 (uM)	RAT Brain FAAH Percent Inhibition @ 0.1 uM	RAT Brain FAAH Percent Inhibition @ 1 uM	Human Brain FAAH (10 uM) Percent Inhibition	Human Brain FAAH IC50 (nM)
126	[5-methoxy-2-methyl-1-[(2E)-3-phenylprop-2-en-1-yl]-1H-indol-3-yl]acetic acid							16	
127	[5-methoxy-2-methyl-1-[[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid				62.6				179.2, 262
128	[5-methoxy-2-methyl-1-[[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							53.39	44.5, 37
129	[5-methoxy-2-methyl-1-[[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							22.67	
130	[6-chloro-1-[[4-(chlorophenyl)carboxyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							4.3	
131	[6-chloro-1-[[5-chloro-2-thienyl]carboxyl]-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid							47.95	28.0, 23.0
132	[6-chloro-1-[[5-chloro-2-thienyl]carboxyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid							19.16	
133	[6-chloro-1-[[5-chloro-2-thienyl]carboxyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							5.08	
134	[6-chloro-1-[[5-chloro-2-thienyl]carboxyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							13.47	
135	[6-chloro-1-[[6-chloropyridin-3-yl]methyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid							12.2	
136	[6-chloro-1-[[4-(trifluoromethoxy)benzoyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid				79.3, 55.0				99, 139.7, 118
137	[6-chloro-2,5-dimethyl-1-[[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							10.9	
138	[6-chloro-2,5-dimethyl-1-[[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							14.3	
139	[6-chloro-5-fluoro-2-methyl-1-[[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							-0.6	
140	[6-chloro-5-hydroxy-2-methyl-1-[[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							-0.94	
141	[6-chloro-5-hydroxy-2-methyl-1-[[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							4.14	
142	[6-chloro-5-methoxy-1-[[4-(methoxy)carboxyl]-2-methyl-1H-indol-3-yl]acetic acid							0.7, 0.7	
143	[6-chloro-5-methoxy-2-methyl-1-[[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							12.1, 24.6	
144	[6-chloro-5-methoxy-2-methyl-1-[[3-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							14.0, 16.1	
145	[6-chloro-5-methoxy-2-methyl-1-[[4-(methoxy)carboxyl]-1H-indol-3-yl]acetic acid							-0.8, -0.8	
146	[6-chloro-5-methoxy-2-methyl-1-[[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							13.89	
147	[6-chloro-5-methoxy-2-methyl-1-[[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid							18.3	
148	[6-fluoro-5-hydroxy-2-methyl-1-[[5-methyl-2-thienyl]carboxyl]-1H-indol-3-yl]acetic acid							2.81, -8.18	
149	[6-fluoro-5-hydroxy-2-methyl-1-[[4-(1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl]acetic acid							3.07, 18.55	
150	[6-fluoro-5-hydroxy-2-methyl-1-[[4-(methylthio)benzoyl]-1H-indol-3-yl]acetic acid							-2.59	

Row	Compound	FAAH Rat brain AMCA IC50 (nm)	FAAH Rat brain AMCA Percent Inhibition (0.1uM)	FAAH Rat brain AMCA Percent Inhibition (1uM)	RAT Brain FAAH IC50 (uM)	RAT Brain FAAH Percent Inhibition @ 0.1uM	RAT Brain FAAH Percent Inhibition @ 1uM	Human Brain FAAH (10uM) Percent Inhibition	Human Brain FAAH IC50 (uM)
151	[6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl] acetic acid							18.83	
152	[6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl] acetic acid							18.58	
153	[6-fluoro-5-methoxy-2-methyl-1-[(5-methyl-2-thienyl)carboxyl]-1H-indol-3-yl] acetic acid							17.12	
154	[6-fluoro-5-methoxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl] acetic acid							15.32	
155	[6-fluoro-5-methoxy-2-methyl-1-[4-(methylthio)benzoyl]-1H-indol-3-yl] acetic acid							6.94	
156	[6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl] acetic acid				48.8				102,97, 89, 14
157	[6-fluoro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl] acetic acid				29.9				86.89, 117
158	1-[1,3-benzothiazol-2-ylmethyl]-5-fluoro-2-methyl-1H-indol-3-carboxylic acid							31.5	
159	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-hydroxyethyl)acetamide				6.2, 9.1				
160	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-phenylethyl)acetamide								>300
161	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-piperidin-1-ylacetamide							28.4	
162	2-[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetamide				302.9, 463, 14.0				
163	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethanol				1.56, 1.66				3.69
164	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl 4-chlorobenzoate								132.4
165	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethyl acetate				1.1				0.97
166	3-[1-(1,3-benzothiazol-2-ylmethyl)-4,6-dichloro-2-methyl-1H-indol-3-yl]propanoic acid							2.8	
167	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-2,5-dimethyl-1H-indol-3-yl]propanoic acid							-1.4	
168	3-[1-(1,3-benzothiazol-2-ylmethyl)-6-chloro-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid							14.6	
169	3-[4,6-dichloro-1-(3-chlorobenzoyl)-2-methyl-1H-indol-3-yl]propanoic acid							16.1	
170	3-[6-chloro-1-(3-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]propanoic acid							11.9	
171	4-[(3-carboxymethyl)-6-chloro-5-methoxy-2-methyl-1H-indol-1-yl]methyl benzoic acid							-18.9	
172	ethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				0.76				
173	ethyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate				0.21, 0.5, 0.53, 0.84				
174	ethyl [6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				2.8, 3.95				56.3, 19.9 ± 34
175	ethyl [6-chloro-1-(4-difluoromethoxybenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate								76.79

Row	Compound	FAAH Rat brain AMCAA IC50 (µM)	FAAH Rat brain AMCAA Percent Inhibition (0.1 µM)	RAT Brain FAAH IC50 (nM)	RAT Brain FAAH Percent Inhibition @ 0.1nM	RAT Brain FAAH Percent Inhibition @ 1µM	Human Brain FAAH (10µM) Percent Inhibition	Human Brain FAAH IC50 (nM)
176	ethyl 4-((1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetyl)amino)butanoate			3.17				2 ± 1.83
177	ethyl N-((1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl)glycinate							208 ± 31
178	ethyl N-((1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetyl)glutamate			2.82			-5.48	43.97, 46 ± 17
179	ethyl N-((6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl)glutamate							
180	isopropyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate			19.5, 24.58				
181	methyl (1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetate		41.2		24	61		
182	methyl (1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetate		39.8		28	71		
183	methyl (1-benzoyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetate		37.1		19	67		
184	methyl (1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetate		26.6		8	54		
185	methyl (6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetate	>10		>100				
186	methyl [1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		42.2		34	74		
187	methyl [1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate				10	75		
188	methyl [1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	0.078	65.3	0.075	50	85		
189	methyl [1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate		24.8		8	38		
190	methyl [1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		43.5		20	70		
191	methyl [1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	0.14, 0.18	58.2	0.10, 0.07	40	83		
192	methyl [1-(4-chlorobenzoyl)-4-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		15.3		9	22		
193	methyl [1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate		22.3		14	35		
194	methyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	0.11	54, 52.1	0.09	32, 27	76, 76		
195	methyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	0.15	53	0.08	40	86		
196	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	0.19	47.7, 57	0.11, 0.33, 0.13, 0.21	32, 34	78, 81		4.84, 1.6 ± 0.2
197	methyl [1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate		27.9, 35.4	0.2	18, 15	67, 62		0.66 ± 0.13
198	methyl [1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate	0.32	46.7	0.17	27	68		
199	methyl [1-(4-fluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		44.7		28	72		
200	methyl [1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	0.16	57.3	0.08	32	75		

Row	Compound	FAAH Rat brain ANICAA IC50 (nm)	FAAH Rat brain ANICAA Percent Inhibition (0.1uM)	FAAH Rat brain ANICAA Percent Inhibition (1uM)	RAT Brain FAAH IC50 (uM)	RAT Brain FAAH Percent Inhibition @ 0.1uM	RAT Brain FAAH Percent Inhibition @ 1uM	Human Brain FAAH (10uM) Percent Inhibition	Human Brain FAAH IC50 (uM)
201	methyl 1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate		24.3	69.5		8	41		
202	methyl 1-(5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetate					29	75		
203	methyl 1-(6-chloro-1-(3-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetate					-1	22		
204	methyl 1-(6-chloro-1-(3-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetate					-6	7		
205	methyl 1-(6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	1.71±1.4 (n=6)			0.7, 2.3, 2.3, 0.72, 2.93				5.51, 5.4±3, 12.6±5.75, 4.2±1.3
206	methyl 1-(6-chloro-1-(4-chlorobenzoyl)-2,5-dimethyl-1H-indol-3-yl]acetate					-7	34		
207	methyl 1-(6-chloro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate					4	27		
208	methyl 1-(6-fluoro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		33.6	79.7		20	58		
209	methyl 1-(6-fluoro-5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetate	0.053	74.8	88.5	0.08	54	82		
210	methyl 1-(6-fluoro-5-methoxy-2-methyl-1-(2-dienylbenzoyl)-1H-indol-3-yl]acetate					-11	21		
211	methyl 1-(6-fluoro-5-methoxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetate	0.32	54.8	79.5	0.11	37	72		
212	methyl 1-(5-chloro-2-thienylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	0.15	51.7	89.9	0.06	36	82		
213	methyl 1-(5-chloro-2-thienylbenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetate		36.2	79.4		24	65		
214	methyl 1-(5-fluoro-2-methyl-1-(3-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetate					-13	-2		
215	methyl 1-(5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetate					-3	27		
216	methyl 1-(5-hydroxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetate					6	42		
217	methyl 1-(5-methoxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetate		43.4	86.8		34	77		
218	methyl 1-(6-chloro-1-(5-chloro-2-thienylbenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetate		37.1	81.1		14	61		
219	methyl 1-(6-chloro-1-(5-chloro-2-thienylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate					-1	22		
220	methyl 1-(6-chloro-1-(5-chloro-2-thienylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate		24	63.6		13	44		
221	methyl 1-(6-chloro-2,5-dimethyl-1-(3-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetate					0	23		
222	methyl 1-(6-chloro-5-methoxy-2-methyl-1-(4-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetate	1	19.6	65.1	0.66	-4	26		
223	methyl 1-(6-fluoro-2,5-dimethyl-1-(3-(trifluoromethoxy)benzoyl)-1H-indol-3-yl]acetate					-2	35		
224	methyl 1-(6-fluoro-5-hydroxy-2-methyl-1-(5-methyl-2-thienylbenzoyl)-1H-indol-3-yl]acetate		43.2	80.8		26	73		
225	methyl 1-(1-(3-benzoxiazol-2-ylmethyl)-5-fluoro-2-methyl-1H-indole-3-carboxylate					-13	-9		

Row	Compound	FAAH Rat brain IC50 (µM)	FAAH Rat brain AMCAA Percent Inhibition (0.1 µM)	FAAH Rat brain AMCAA Percent Inhibition (1 µM)	RAT Brain FAAH IC50 (nM)	RAT Brain FAAH Percent Inhibition @ 0.1 µM	RAT Brain FAAH Percent Inhibition @ 1 µM	Human Brain FAAH (10 nM) Percent Inhibition	Human Brain FAAH IC50 (nM)
226	methyl N-((1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetate)-D-alaninate				2.22				
227	N-((1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate)glycine								139 ± 8.5
228	N-((6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate)glycine							-18.7	
229	propyl 1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl acetate				1.35, 4.12				36.46
230	propyl (6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate								
231	sec-butyl 1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl acetate				13.27				
232	sec-butyl (6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate								88.6

row	Chemical Name	Rat FAAH IC ₅₀ (μM)	Human FAAH IC ₅₀ (μM)
1	(1-benzyl-5-methoxy-2-methyl-1H-indol-3-yl)(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	10-50
2	(2E)-3-[5-chloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl]acrylic acid	1-10	not determined
3	(5-methoxy-1,2-dimethyl-1H-indol-3-yl)(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	>100
4	(5-methoxy-2-methyl-1-phenyl-1H-indol-3-yl)(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	50-100
5	[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)methanone	<1	<1
6	[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	<1	<1
7	[1-(2-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	50-100
8	[1-(3,4-dichlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	10-50
9	[1-(3,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	1-10
10	[1-(3,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone O-methylloxime	10-50	>100
11	[1-(3,5-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	10-50
12	[1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	50-100	10-50
13	[1-(4-bromobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	<1	1-10
14	[1-(4-bromobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	1-10
15	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	>100
16	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](1,3-oxazolol[4,5-b]pyridin-2-yl)methanone	<1	<1
17	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)methanone	<1	<1
18	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-phenyl-1,3,4-oxadiazol-2-yl)methanone	1-10	1-10
19	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	<1	<1
20	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-2-thienyl)methanone	1-10	50-100
21	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-3-yl-1,3,4-oxadiazol-2-yl)methanone	<1	1-10
22	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-4-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	1-10
23	[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-(2-furyl)-1,3,4-oxadiazol-2-yl)methanone	1-10	<1
24	[1-(4-chlorophenyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	50-100	10-50
25	[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	1-10
26	[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	50-100
27	[5-chloro-1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	50-100
28	[5-chloro-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	>100
29	[5-hydroxy-2-methyl-1-(4-methylbenzyl)-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	10-50
30	[5-methoxy-1-(2-methoxybenzyl)-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	>100	>100
31	[5-methoxy-1-(3-methoxybenzyl)-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	>100
32	[5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl](3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)methanone	<1	<1
33	[5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl](5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	<1	1-10

row	Chemical Name	Rat FAAH IC ₅₀ (μM)	Human FAAH IC ₅₀ (μM)
34	[5-methoxy-1-(4-methoxyphenyl)-2-methyl-1H-indol-3-yl]-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	>100	>100
35	[5-methoxy-2-methyl-1-(4-methylbenzyl)-1H-indol-3-yl]-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	1-10
36	[1-(4-methylphenyl)sulfonyl]-1H-indol-3-yl]-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	>100
37	[1-(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl]-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	1-10
38	[1-(2-(4-chlorophenyl)ethyl)-5-methoxy-2-methyl-1H-indol-3-yl]-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	10-50
39	[1-(3-(4-chlorophenyl)propyl)-5-methoxy-2-methyl-1H-indol-3-yl]-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	50-100	>100
40	[5-methoxy-2-methyl-1-(4-(trifluoromethoxy)benzyl)-1H-indol-3-yl]-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	50-100
41	[5-methoxy-2-methyl-1-(4-(trifluoromethyl)benzyl)-1H-indol-3-yl]-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	1-10	10-50
42	1-(4-chlorobenzyl)-N,5-dimethoxy-N,2-dimethyl-1H-indole-3-carboxamide	1-10	10-50
43	1-(4-chlorobenzyl)-N-cyclohexyl-5-methoxy-2-methyl-1H-indole-3-carboxamide	50-100	>100
44	1-(4-chlorobenzyl)-N-cyclopropyl-5-methoxy-2-methyl-1H-indole-3-carboxamide	10-50	>100
45	1-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-morpholin-4-yl-2-oxoethanone	10-50	10-50
46	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-(5-pyridin-2-yl-1,3,4-oxadiazol-2-yl)methanone	10-50	50-100
47	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxo-N-piperidin-1-ylacetamide	1-10	1-10
48	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	<1	<1
49	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	1-10	1-10
50	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclopropyl-2-oxoacetamide	1-10	10-50
51	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-2-ylacetamide	1-10	1-10
52	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	<1	<1
53	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-piperidin-1-ylacetamide	1-10	1-10
54	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-2-ylacetamide	<1	<1
55	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1	<1
56	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1	<1
57	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-hydroxypyridin-2-yl)-2-oxoacetamide	<1	<1
58	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	<1	<1
59	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclohexylacetamide	1-10	10-50
60	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclopropyl-2-oxoacetamide	1-10	1-10
61	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclopropylacetamide	10-50	>100
62	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-methoxy-N-methylacetamide	1-10	1-10
63	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	<1	<1
64	3-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1,1,1-trifluoroacetone	1-10	10-50
65	methyl (1-benzoyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetate	<1	1-10
66	methyl (1-benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetate	<1	1-10

row	Chemical Name	Rat FAAH IC ₅₀ (μM)	Human FAAH IC ₅₀ (μM)
67	methyl (2E)-3-[5-chloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl]acrylate	<1	1-10
68	methyl [1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]oxoacetate	1-10	1-10
69	methyl [1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetate	<1	not determined
70	methyl [6-fluoro-5-hydroxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetate	<1	not determined
71	methyl [6-fluoro-5-methoxy-2-methyl-1-(4-methylbenzoyl)-1H-indol-3-yl]acetate	<1	not determined
72	methyl [5,6-dichloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl]acetate	1-10	>100
73	methyl [5-chloro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl]acetate	<1	10-50
74	methyl [6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzyl]-1H-indol-3-yl]acetate	<1	not determined
75	methyl 1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indole-3-carboxylate	1-10	10-50
76	N-cyclohexyl-2-[1-(2,4-dichlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	1-10
77	N-cyclohexyl-2-[1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	10-50	1-10
78	N-cyclohexyl-2-[1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	10-50
79	N-cyclopropyl-2-[1-(2,4-dichlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	1-10
80	N-cyclopropyl-2-[1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	>100	>100
81	N-cyclopropyl-2-[1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	10-50
82	URB597 (positive control)	<1	<1

FIGURE 9C

Row	IUPAC Name	Rat Brain Extract FAAH IC50 (uM)	Human brain FAAH Extract IC50 (uM)
1	(Z)-1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl-(5-pyridin-2-yl)-1,3,4-oxadiazol-2-yl)methanone O-methylloxime	<1	1-10
2	(Z)-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl-(5-pyridin-2-yl)-1,3,4-oxadiazol-2-yl)methanone O-methylloxime	<1	1-10
3	1-(4-bromobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl-(5-pyridin-2-yl)-1,3,4-oxadiazol-2-yl)methanone O-methylloxime	<1	1-10
4	5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl-(5-pyridin-2-yl)-1,3,4-oxadiazol-2-yl)methanone O-methylloxime	<1	1-10
5	1-(1-(2,4-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl)-2-morpholin-4-yl-2-oxoethanone	1-10	1-10
6	1-(1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)-2-morpholin-4-yl-2-oxoethanone	10-50	10-50
7	2-(1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)-2-oxo-N-phenylacetamide	not determined	<1
8	2-(1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)-2-oxo-N-pyridin-3-ylacetamide	<1	<1
9	2-(1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)-2-oxo-N-pyridin-4-ylacetamide	<1	<1
10	2-(1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)-2-oxo-N-pyrimidin-4-ylacetamide	not determined	<1
11	2-(1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-(3-methoxyphenyl)-2-oxoacetamide	not determined	<1
12	2-(1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-(5-methoxy-2-methylphenyl)-2-oxoacetamide	not determined	1-10
13	2-(1-(2,4-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl)-2-oxo-N-phenylacetamide	<1	<1
14	2-(1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl)-2-oxo-N-piperidin-1-ylacetamide	1-10	1-10
15	2-(1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl)-2-oxo-N-pyridin-3-ylacetamide	<1	<1
16	2-(1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl)-2-oxo-N-pyridin-4-ylacetamide	<1	<1
17	2-(1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl)-N-cyclohexyl-2-oxoacetamide	<1	<1
18	2-(1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl)-2-oxo-N-phenylacetamide	10-50	10-50
19	2-(1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl)-2-oxo-N-pyridin-3-ylacetamide	1-10	1-10
20	2-(1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl)-2-oxo-N-pyridin-4-ylacetamide	10-50	<1
21	2-(1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl)-N-cyclohexyl-2-oxoacetamide	>100	>100
22	2-(1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl)-N-cyclopropyl-2-oxoacetamide	10-50	10-50
23	2-(1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl)-2-oxo-N-phenylacetamide	not determined	<1
24	2-(1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl)-2-oxo-N-pyridin-3-ylacetamide	not determined	<1
25	2-(1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl)-2-oxo-N-pyridin-4-ylacetamide	not determined	<1
26	2-(1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl)-2-oxo-N-pyrimidin-4-ylacetamide	not determined	<1
27	2-(1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl)-N-(3-chlorophenyl)-2-oxoacetamide	not determined	<1
28	2-(1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl)-N-cyclohexyl-2-oxoacetamide	1-10	1-10
29	2-(1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl)-N-cyclopropyl-2-oxoacetamide	1-10	10-50
30	2-(1-(4-chlorobenzyl)-5-ethoxy-2-methyl-1H-indol-3-yl)-2-oxo-N-phenylacetamide	<1	<1
31	2-(1-(4-chlorobenzyl)-5-ethoxy-2-methyl-1H-indol-3-yl)-2-oxo-N-pyridin-4-ylacetamide	<1	not determined
32	2-(1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl)-2-oxo-N-phenylacetamide	not determined	<1
33	2-(1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl)-2-oxo-N-pyridin-4-ylacetamide	<1	<1
34	2-(1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl)-2-oxo-N-pyridin-2-ylacetamide	1-10	1-10

Row	IUPAC Name	Rat Brain Extract FAAH IC50 (uM)	Human brain FAAH Extract IC50 (uM)
35	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	not determined	<1
36	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	not determined	<1
37	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	not determined	<1
38	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1	<1
39	2-[1-(4-chlorobenzyl)-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl]-2-oxo-N-pyridin-2-ylacetamide	10-50	1-10
40	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-(phenylsulfonyl)acetamide	>100	>100
41	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	<1	<1
42	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-piperidin-1-ylacetamide	1-10	1-10
43	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-2-ylacetamide	<1	<1
44	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1	<1
45	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1	<1
46	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1	<1
47	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-chlorophenyl)-2-oxoacetamide	1-10	<1
48	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1	<1
49	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-fluorophenyl)-2-oxoacetamide	<1	<1
50	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxyphenyl)-2-oxoacetamide	>100	10-50
51	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3,5-dichlorophenyl)-2-oxoacetamide	not determined	<1
52	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1	<1
53	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-fluorophenyl)-2-oxoacetamide	<1	<1
54	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-hydroxypyridin-2-yl)-2-oxoacetamide	<1	<1
55	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1	<1
56	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4,5-dimethyl-1,3-thiazol-2-yl)-2-oxoacetamide	>100	>100
57	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-chlorophenyl)-2-oxoacetamide	<1	<1
58	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-fluorophenyl)-2-oxoacetamide	<1	<1
59	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-methoxyphenyl)-2-oxoacetamide	<1	<1
60	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(6-methoxypyrimidin-4-yl)-2-oxoacetamide	<1	<1
61	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	<1	<1
62	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclohexyl-N-methyl-2-oxoacetamide	1-10	<1
63	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclopropyl-2-oxoacetamide	1-10	1-10
64	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-methyl-2-oxo-N-phenylacetamide	1-10	<1
65	2-[1-(4-chlorobenzyl)-7-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	not determined	>10
66	2-[1-(4-chlorobenzyl)-7-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	not determined	>10
67	2-[1-(4-chlorobenzyl)-7-methoxy-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	not determined	>10
68	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1	<1

Figure 9C

Row	IUPAC Name	Rat Brain Extract FAAH IC50 (uM)	Human brain FAAH Extract IC50 (uM)
69	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1	<1
70	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1	<1
71	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1	<1
72	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1	<1
73	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1	<1
74	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-piperidin-1-ylacetamide	10-50	1-10
75	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-2-ylacetamide	<1	<1
76	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	not determined	<1
77	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	not determined	<1
78	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	not determined	<1
79	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	not determined	<1
80	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	not determined	<1
81	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	<1	<1
82	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclopropyl-2-oxoacetamide	1-10	1-10
83	N-(2,4-dichlorobenzyl)-2-[1-(2,4-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	>100	>100
84	N-(3-chlorophenyl)-2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxoacetamide	not determined	<1
85	N-(4-chlorobenzyl)-2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxoacetamide	>100	>100
86	N-benzyl-2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	1-10
87	N-cyclohexyl-2-[1-(2,4-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxoacetamide	<1	<1
88	N-cyclohexyl-2-[1-(2,4-dichlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	1-10
89	N-cyclohexyl-2-[1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	10-50	1-10
90	N-cyclohexyl-2-[1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	10-50
91	N-cyclopropyl-2-[1-(2,4-dichlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	1-10
92	N-cyclopropyl-2-[1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	>100	10-50
93	N-cyclopropyl-2-[1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10	10-50
94	URB597 (positive control)	<1	<1

FIGURE 9D

Row	IUPAC Name	Human Brain FAAH extract IC50 (µm)
1	1-[1-(2,4-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-morpholin-4-yl-2-oxoethanone	1-10
2	1-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-morpholin-4-yl-2-oxoethanone	10-50
3	2-(1-benzyl-2,5-dimethyl-1H-indol-3-yl)-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
4	2-(1-benzyl-2-methyl-1H-indol-3-yl)-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
5	2-(1-benzyl-5-methoxy-2-methyl-1H-indol-3-yl)-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
6	2-(5-methoxy-2-methyl-1H-indol-3-yl)-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	>5
7	2-[1-(2,4-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
8	2-[1-(2,4-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(3-fluorophenyl)-2-oxoacetamide	<1
9	2-[1-(2,4-dichlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
10	2-[1-(2,4-dichlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
11	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	<1
12	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1
13	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
14	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
15	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
16	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
17	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4,5-dimethyl-1,3-thiazol-2-yl)-2-oxoacetamide	<1
18	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(5-methoxy-2-methylphenyl)-2-oxoacetamide	1-10
19	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(5-methyl-1,3-thiazol-2-yl)-2-oxoacetamide	<1
20	2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(5-methylisoxazol-3-yl)-2-oxoacetamide	<1
21	2-[1-(2,4-difluorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1

Row	IUPAC Name	Human Brain FAAH extract IC50 (µm)
22	2-[1-(2,4-difluorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
23	2-[1-(2,4-difluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
24	2-[1-(2-chloro-4-fluorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
25	2-[1-(2-chloro-4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
26	2-[1-(2-chloro-4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
27	2-[1-(2-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
28	2-[1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
29	2-[1-(4-chloro-2-fluorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
30	2-[1-(4-chloro-2-fluorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
31	2-[1-(4-chloro-2-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
32	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	<1
33	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxo-N-piperidin-1-ylacetamide	1-10
34	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1
35	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
36	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
37	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
38	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
39	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1
40	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
41	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	<1
42	2-[1-(4-chlorobenzyl)-2,5-dimethyl-1H-pyrrol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1

Row	IUPAC Name	Human Brain FAAH extract IC50 (µm)
43	2-[1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl]-2-oxo-N-phenylacetamide	10-50
44	2-[1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	1-10
45	2-[1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
46	2-[1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	>100
47	2-[1-(4-chlorobenzyl)-2-isopropyl-5-methoxy-1H-indol-3-yl]-N-cyclopropyl-2-oxoacetamide	10-50
48	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	<1
49	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1
50	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
51	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
52	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
53	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
54	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1
55	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
56	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	1-10
57	2-[1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclopropyl-2-oxoacetamide	10-50
58	2-[1-(4-chlorobenzyl)-5-ethoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	<1
59	2-[1-(4-chlorobenzyl)-5-ethoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
60	2-[1-(4-chlorobenzyl)-5-ethoxy-2-methyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
61	2-[1-(4-chlorobenzyl)-5-ethoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
62	2-[1-(4-chlorobenzyl)-5-ethoxy-2-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
63	2-[1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1

Row	IUPAC Name	Human Brain FAAH extract IC50 (um)
64	2-[1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
65	2-[1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
66	2-[1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
67	2-[1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1
68	2-[1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
69	2-[1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	<1
70	2-[1-(4-chlorobenzyl)-5-hydroxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
71	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-2-ylacetamide	<1
72	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1
73	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
74	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
75	2-[1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
76	2-[1-(4-chlorobenzyl)-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl]-2-oxo-N-pyridin-2-ylacetamide	1-10
77	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-[3-(trifluoromethoxy)phenyl]acetamide	<1
78	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-[3-(trifluoromethyl)phenyl]acetamide	<1
79	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-1,3-thiazol-2-ylacetamide	<1
80	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-phenylacetamide	<1
81	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-piperidin-1-ylacetamide	1-10
82	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-2-ylacetamide	<1
83	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1
84	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1

Row	IUPAC Name	Human Brain FAAH extract IC50 (µm)
85	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-oxo-N-pyrimidin-4-yl)acetamide	<1
86	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2,6-difluorophenyl)-2-oxoacetamide	<1
87	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-chlorophenyl)-2-oxoacetamide	<1
88	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
89	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-ethoxypyridin-4-yl)-2-oxoacetamide	<1
90	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-fluorophenyl)-2-oxoacetamide	<1
91	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-fluoropyridin-4-yl)-2-oxoacetamide	<1
92	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxyphenyl)-2-oxoacetamide	10-50
93	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
94	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3,5-dichlorophenyl)-2-oxoacetamide	<1
95	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-chloro-4-fluorophenyl)-2-oxoacetamide	<1
96	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1
97	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-ethoxyphenyl)-2-oxoacetamide	<1
98	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-ethylphenyl)-2-oxoacetamide	<1
99	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-fluorophenyl)-2-oxoacetamide	<1
100	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-fluoropyridin-4-yl)-2-oxoacetamide	<1
101	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-hydroxypyridin-2-yl)-2-oxoacetamide	<1
102	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
103	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-methylphenyl)-2-oxoacetamide	<1
104	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4,5-dimethyl-1,3-thiazol-2-yl)-2-oxoacetamide	>100
105	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-chlorophenyl)-2-oxoacetamide	<1

Row	IUPAC Name	Human Brain FAAH extract IC50 (um)
106	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-fluorophenyl)-2-oxoacetamide	<1
107	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-methoxyphenyl)-2-oxoacetamide	<1
108	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-methoxypyridin-2-yl)-2-oxoacetamide	<1
109	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-methyl-1,3-thiazol-2-yl)-2-oxoacetamide	<1
110	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(5-methoxypyridin-2-yl)-2-oxoacetamide	<1
111	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(5-methylisoxazol-3-yl)-2-oxoacetamide	<1
112	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(6-ethoxypyridin-3-yl)-2-oxoacetamide	1-10
113	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(6-methoxypyridin-2-yl)-2-oxoacetamide	<1
114	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(6-methoxypyridin-3-yl)-2-oxoacetamide	<1
115	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(6-methoxypyrimidin-4-yl)-2-oxoacetamide	<1
116	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	<1
117	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclohexyl-N-methyl-2-oxoacetamide	<1
118	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-cyclopropyl-2-oxoacetamide	1-10
119	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-isoxazol-3-yl-2-oxoacetamide	<1
120	2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-methyl-2-oxo-N-phenylacetamide	<1
121	2-[1-(4-chlorobenzyl)-7-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	>10
122	2-[1-(4-chlorobenzyl)-7-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	>10
123	2-[1-(4-chlorobenzyl)-7-methoxy-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	>10
124	2-[1-(4-fluorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
125	2-[1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
126	2-[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1

Row	IUPAC Name	Human Brain FAAH extract IC50 (um)
127	2-[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(3-fluorophenyl)-2-oxoacetamide	<1
128	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-3-ylacetamide	<1
129	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
130	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
131	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
132	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
133	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1
134	2-[2-chloro-1-(4-chlorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
135	2-[2-chloro-1-(4-chlorobenzyl)-5-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
136	2-[2-chloro-1-(4-chlorobenzyl)-5-methyl-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
137	2-[2-chloro-1-(4-chlorobenzyl)-5-methyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
138	2-[2-chloro-1-(4-chlorobenzyl)-5-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
139	2-[2-chloro-1-(4-chlorobenzyl)-5-methyl-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1
140	2-[2-chloro-1-(4-chlorobenzyl)-5-methyl-1H-indol-3-yl]-N-(3-fluorophenyl)-2-oxoacetamide	<1
141	2-[2-chloro-1-(4-chlorobenzyl)-5-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
142	2-[2-chloro-1-(4-fluorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
143	2-[2-chloro-1-(4-fluorobenzyl)-5-methoxy-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
144	2-[2-chloro-1-(4-fluorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
145	2-[2-chloro-1-(4-fluorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
146	2-[2-chloro-1-(4-fluorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1
147	2-[2-chloro-1-(4-fluorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(3-fluorophenyl)-2-oxoacetamide	<1

Row	IUPAC Name	Human Brain FAAH extract IC50 (µm)
148	2-[2-chloro-1-(4-fluorobenzyl)-5-methoxy-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
149	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-piperidin-1-ylacetamide	1-10
150	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-2-ylacetamide	<1
151	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyridin-4-ylacetamide	<1
152	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxo-N-pyrimidin-4-ylacetamide	<1
153	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-chloropyridin-4-yl)-2-oxoacetamide	<1
154	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
155	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(3-chlorophenyl)-2-oxoacetamide	<1
156	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-(3-methoxyphenyl)-2-oxoacetamide	<1
157	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclohexyl-2-oxoacetamide	<1
158	2-[5-chloro-1-(4-chlorobenzyl)-2-methyl-1H-indol-3-yl]-N-cyclopropyl-2-oxoacetamide	1-10
159	2-[5-chloro-1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
160	2-[5-fluoro-1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
161	2-[5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
162	2-[5-methoxy-2-methyl-1-(4-methylbenzyl)-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
163	2-[1-[(6-chloropyridin-3-yl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
164	2-[5-methoxy-2-methyl-1-(4-(trifluoromethoxy)benzyl)-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	1-10
165	2-[5-methoxy-2-methyl-1-(4-(trifluoromethyl)benzyl)-1H-indol-3-yl]-N-(2-methoxypyridin-4-yl)-2-oxoacetamide	<1
166	N-(2-chloropyridin-4-yl)-2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxoacetamide	<1
167	N-(2-chloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxoacetamide	<1
168	N-(2-chloropyridin-4-yl)-2-[5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	<1

Row	IUPAC Name	Human Brain FAAH extract IC50 (um)
169	N-(3-chlorophenyl)-2-[1-(2,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxoacetamide	<1
170	N-(3-chlorophenyl)-2-[1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxoacetamide	<1
171	N-(3-chlorophenyl)-2-[5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	<1
172	N-(3-chlorophenyl)-2-[1-(6-chloropyridin-3-yl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxoacetamide	<1
173	N-(3-fluorophenyl)-2-[5-methoxy-1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	<1
174	N-benzyl-2-[1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10
175	N-cyclohexyl-2-[1-(2,4-dichlorobenzyl)-2,5-dimethyl-1H-indol-3-yl]-2-oxoacetamide	<1
176	N-cyclohexyl-2-[1-(2,4-dichlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10
177	N-cyclohexyl-2-[1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10
178	N-cyclohexyl-2-[1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	10-50
179	N-cyclopropyl-2-[1-(2,4-dichlorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	1-10
180	N-cyclopropyl-2-[1-(4-fluorobenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	>100
181	N-cyclopropyl-2-[1-(4-methoxybenzyl)-2-methyl-1H-indol-3-yl]-2-oxoacetamide	10-50
182	URB597 (positive control)	<1

FIGURE 9D

Row	Compound	Displacement @ 10 uM	Displacement @ 1 uM
1	{6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid ^A	39%	14%
2	{6-fluoro-5-hydroxy-2-methyl-1-[4-[(trifluoromethyl)thio]benzoyl]-1H-indol-3-yl}acetic acid ^A	13%	12%
3	{1-(1,3-benzothiazol-2-yl)methyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid ^A	35%	10%
4	{6-chloro-5-methoxy-2-methyl-1-[4-[(trifluoromethyl)thio]benzyl]-1H-indol-3-yl}acetic acid ^A	43%	19%
5	{6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid ^A	35%	10%
6	{6-chloro-2,5-dimethyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid ^B	72%	13%
7	{6-chloro-5-methoxy-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid ^B	78%	18%
8	{6-chloro-5-fluoro-2-methyl-1-[3-(trifluoromethoxy)benzyl]-1H-indol-3-yl}acetic acid ^B	72%	16%

A - Ramatroban control exhibited 91% displacement at 10 mM and 88% displacement at 1 mM

B - Ramatroban control exhibited 97% displacement at 10 mM and 96% displacement at 1 mM